Mount Sinai

MSSM

MOUNT SINAI SCHOOL OF MEDICINE

THE FRIEDMAN BRAIN INSTITUTE

ACCELERATING SCIENCE–ADVANCING MEDICINE

The Friedman Brain Institute is one of the world's premier institutions dedicated to advancing our understanding of brain and spinal cord disorders, and driving innovative approaches to new treatments and diagnostic tests, through translational research.

The nervous system is the last frontier of the molecular revolution in medicine. The past decade has witnessed extraordinary advances in experimental tools to study the brain and spinal cord. Impressive strides have been made in understanding how the nervous system functions under normal conditions and malfunctions in disease. We are now poised to take advantage of this growing knowledge to develop fundamentally improved diagnostic tests, treatments, and ultimately, cures and preventive measures for disorders of the brain and spinal cord. The goal of The Friedman Brain Institute—or FBI—at The Mount Sinai Medical Center is to play a leading role, nationally and internationally, in this exciting endeavor. To help meet this goal, in 2012 the FBI will add more than 55,000 square feet of laboratory space when Mount Sinai's new Center for Science and Medicine opens.

The FBI is distinguished by its multidisciplinary research and clinical efforts. These span basic molecular and genetic research of animal models of nervous system disorders in the laboratory and investigations of human populations in the clinic. New knowledge from animal studies drives clinical investigations, while fresh insight from clinical studies provides feedback and helps guide further explorations. This broad-based approach, utilizing a wide range of state-of-the-art methodologies, involves research and clinical work across numerous basic science and clinical departments at Mount Sinai.

The FBI's work is carried out across ten highly interactive Centers of Excellence, some focused on specific disease states, others focused on basic knowledge in neuroscience or on methodologies and experimental approaches. Each Center is headed by a chief, as listed on page 2.

Ultimately, the success of the FBI will rely on its unique ability to develop and employ innovative approaches in its science—both in laboratory animals and in humans. For the first time, investigators will be able to think about correcting genetic abnormalities in the brain and spinal cord, and rescuing or repairing threatened nerve cells. In the years ahead, Mount Sinai's FBI will be a leader in making these revolutionary changes in clinical neuroscience a reality.

WWW.MOUNTSINAI.ORG/FBI

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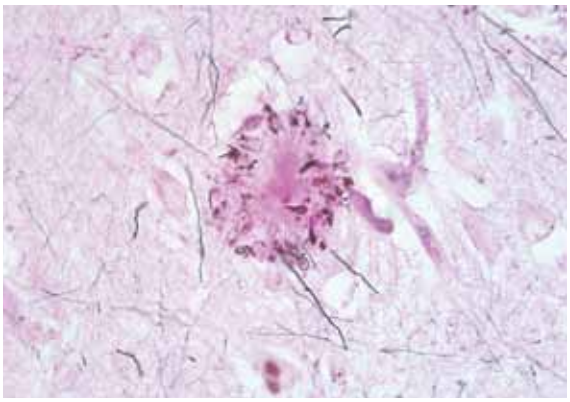
INSIDE THIS ISSUE



The amyloid plaque. The brains of Alzheimer's patients become riddled with these structures as the disease progresses. The dark purplish and black string-like structures are damaged neuron axons and dendrites.

MEDICAL MILESTONES

A Paradigm Shift in Alzheimer's Disease Research

Alzheimer's disease (AD) is the most common cause of dementia, a state literally meaning "lost ability to think." Dementia affects half of the over-85 population, and AD is responsible for about two-thirds of all dementia. The signature change in the brains of AD patients is the buildup of structures called plaques that are composed of a protein, amyloid-β.

Amyloid-β normally floats around and between brain cells, but in AD, amyloid-β sticks together and forms two abnormal structures: 1) string-like fibers that build up to form amyloid plaques, and 2) less organized clumps of multiple amyloid-β units called oligomers. Oligomers and plaques have different effects on the brain. While most emphasis in the field has been on plaques, and ways to reduce plaque buildup, recent research at The Mount Sinai Medical Center supports the novel view that oligomers may be the more important villain.

continued on page 2

Centers of Excellence Chiefs at The Friedman Brain Institute

Brain Aging
Patrick R. Hof, MD, Professor of Neuroscience, Geriatrics and Palliative Medicine, and Ophthalmology

Brain Imaging
Chief to be named

Cognition & Neural Plasticity
Cristina Alberini, PhD, Professor of Neuroscience, Psychiatry, and Structural and Chemical Biology; and Matthew Shapiro, PhD, Associate Professor of Neuroscience and Geriatrics and Palliative Medicine

Computational & Systems Neuroscience
Ehud Kaplan, PhD, Professor of Neuroscience, Structural and Chemical Biology, and Ophthalmology

Mood & Motivation
Yasmin L. Hurd, PhD, Director of the MD/PhD program at Mount Sinai School of Medicine, Professor of Pharmacology and Systems Therapeutics, Psychiatry, and Neuroscience

Myelin Disorders: Mechanisms & Repair
Patrizia Casaccia, MD, PhD, Professor of Neuroscience, Genetics and Genomic Sciences, and Neurology

Neural Injury & Repair
Chief to be named

Neurodegeneration
Samuel E. Gandy, MD, PhD, Professor of Neurology and Psychiatry

Neurodevelopmental Disorders
Joseph D. Buxbaum, MSc, PhD, Professor of Psychiatry, Genetics and Genomic Sciences, and Neuroscience

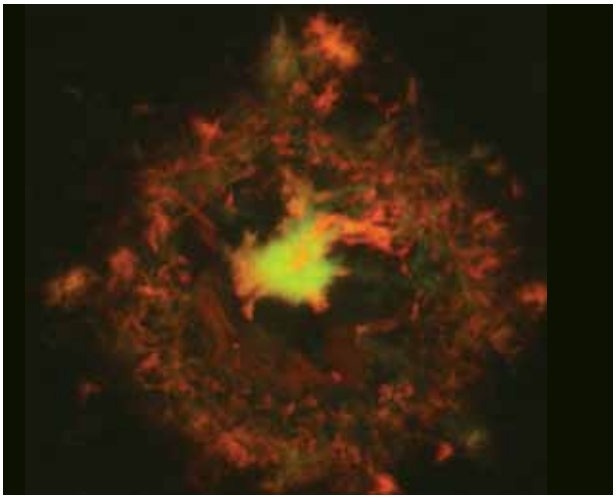
Novel Approaches to Neurodiagnostics & Neurotherapeutics
Giulio M. Pasinetti, MD, PhD, Professor of Neurology, Psychiatry, Neuroscience, and Geriatrics and Palliative Medicine

A Paradigm Shift in Alzheimer's Disease Research, continued from page 1

The first clue that oligomers are detrimental comes from experiments that showed that extracts from the brains of AD patients—rich in oligomers but not plaques—are highly toxic to normal nerve cells grown in culture. Direct proof of this hypothesis comes from recent work in the laboratories of Michelle Ehrlich, MD, Professor of Pediatrics and Neurology and laboratory Principal Investigator in the FBI, and of Samuel E. Gandy, MD, PhD, Professor of Neurology and Psychiatry, and chief of the FBI's Center of Excellence on Neurodegeneration. Dr. Ehrlich and colleagues created a mouse with a gene that expresses an abnormal form of amyloid-β, which causes AD in humans. These mice do not develop plaque, but exhibit memory deficits.

However, further investigation shows that the mice have elevated levels of oligomers, and that the level of oligomers predicts the severity of memory impairment. Dr. Ehrlich next added a second AD gene to the mice, which causes plaques to develop on top of the oligomers. These mice are no worse off than the "oligomer-only" mice, and again, the severity of memory deficits is related to levels of oligomers, with no relationship to plaque buildup. This leads the scientists to conclude that oligomers are more important than plaques in causing memory deficits—the hallmark of AD.

These findings are now driving fundamental new approaches to AD in the clinic. One goal is to explore ways to reduce oligomer burden, or accelerate clearance of oligomers, in the genetic mutant mice. New experimental treatments developed and optimized in these mouse models can be applied to AD patients. Another goal is to develop brain scans that selectively measure oligomer buildup even before memory problems develop, which could be used for early diagnosis of the illness.



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Dr. Gandy, together with Patrick Hof, MD, Vice Chair and Professor of Neuroscience, and Dara Dickstein, PhD, Assistant Professor of Neuroscience, is studying new dyes that change color depending on their environments. Here, an amyloid plaque emits a yellowish-green color from the core and an orange color from the more distal structure called the corona. These dyes may one day enable scientists to visualize amyloid-β oligomers. FBI scientists are spearheading worldwide efforts of Alzheimer's researchers to develop such oligomer-imaging dyes.

A History of Breakthroughs at Mount Sinai

1887	1910	1978	1984	1987
Became first institution to describe Tay-Sachs disease	Sponsored first continuously running Department of Physical Medicine and Rehabilitation in the U.S.	Developed first use of cholinesterase inhibitors to improve cognition	Established one of five original Alzheimer's Disease Research Centers in the nation	Established one of five original Traumatic Brain Injury (TBI) Model Systems of Care in the nation

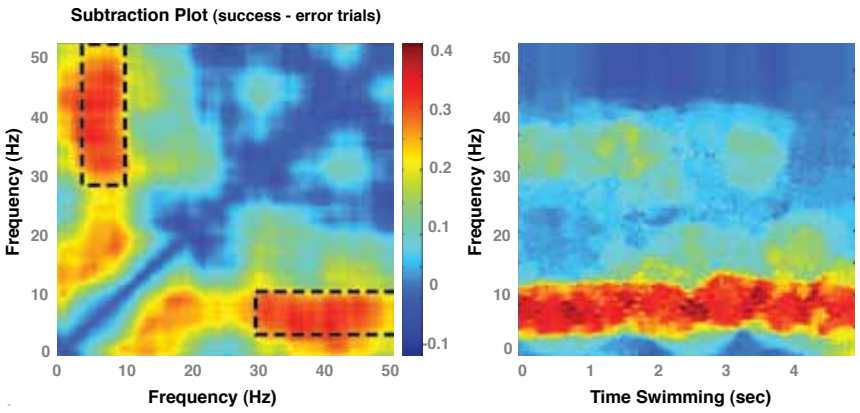
The Friedman Brain Institute Scientists Discover Mechanisms of Memory Retrieval

What did you do yesterday? What will you do tomorrow? We can recall the past and imagine the future using episodic memory, a process that requires specific brain networks involving the hippocampus. These networks fail in memory disorders, such as Alzheimer's disease, but recent work has found mechanisms of episodic memory that suggest potential new treatments.

The hippocampus communicates with other regions of cerebral cortex and several subcortical structures. During everyday events, cortical and subcortical signals arrive in the hippocampus, where neurons respond with unique firing patterns. These patterns are "stored" as changes in strength at particular hippocampal synapses. For example, cortical signals representing the image of a face and the sound of a name connect to overlapping sets of hippocampal neurons. If the face and name are important, those connections strengthen so that, later, either hearing the name or seeing the face would activate the same hippocampal cells. The hippocampus activates the same brain regions that provide its input, so seeing a familiar face could, via hippocampal circuits, activate cortical neurons that represent a name.

To work properly, some mechanism must coordinate the widely distributed brain networks that communicate with the hippocampus. Oscillations in brain activity appear to be crucial. Like EEGs (electroencephalograms) recorded from the scalp, local field potentials (LFPs) are synchronous electrical activity recorded from a brain region where groups of cells become excited (or inhibited) at the same time. LFPs occur at different frequencies, corresponding to local and distant signals. In hippocampus, theta (4-12 Hz) and gamma (30-100 Hz) frequencies are prominent, and each is important for hippocampal function and memory. It was theorized in 1995 that items are ordered in memory by organizing cycles of hippocampal gamma and theta activity with LFPs occurring elsewhere in the brain. This theory predicts that memory depends upon simultaneous and correlated rhythms, but has remained untested until recently.

Matthew Shapiro, PhD, Associate Professor of Neuroscience, and co-Chief of the FBI's Center of Excellence on Cognition & Neural Plasticity, demonstrated that coincident theta and gamma rhythms are required for memory retrieval. When rats were trained in a water maze to remember the location of a hidden escape platform, initially, the rat searched for and escaped onto a platform hidden underwater. On subsequent trials, it used memory to return directly to the platform. As the platform location changes daily, the rat has to learn a new target each day. The Shapiro laboratory found that neither theta nor gamma rhythm alone predicted memory performance, but the correlation of the two (theta-gamma correlations or TGC) strongly predicted memory performance from one trial to the next. TGC was high when rats remembered the platform location and swam directly to it, but was low when memory failed and rats swam to the wrong place.



LEFT: Differences in theta-gamma correlations (TGC) in the hippocampus between memory success and failure. The dashed boxes indicate robust TGC, which occur during successful memory trials.

RIGHT: Hippocampal rhythms in a rat using memory to find a hidden goal. Frequency of hippocampal rhythms (from 0 to 50 Hz), and rhythm intensity (or power) illustrated by color (red, high power; blue, low power), are plotted against the time it takes a rat to swim to its goal. The red band spanning 4–12 Hz reveals powerful theta rhythm; yellow "clouds" between 25 and 45 Hz show gamma.

Pharmacological inactivation of the medial septum (a major input to hippocampus) impaired memory and reduced TGC. In contrast, direct electrical stimulation that increased TGC partially rescued memory performance in these animals.

The results show that hippocampal TGC accompany memory retrieval and provide the first direct evidence that neural networks involving the hippocampus are organized in time to retrieve recent memories. The findings suggest novel ways of improving cognition in patients with memory disorders: Deep brain stimulation promoting TGC is one potential approach, as is exploiting molecular events downstream of TGC to enhance memory.

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1995
Developed first use of deep brain stimulation of subthalamic nucleus to treat Parkinson's disease

2001
Demonstrated abnormalities in brain oligodendrocytes in schizophrenia

2003
Discovered estrogen's protective effects against synapse and cognitive loss in aging female primates

2004
Identified one of the first common gene variants linked to autism

2006
Discovered first biomarkers for amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease)

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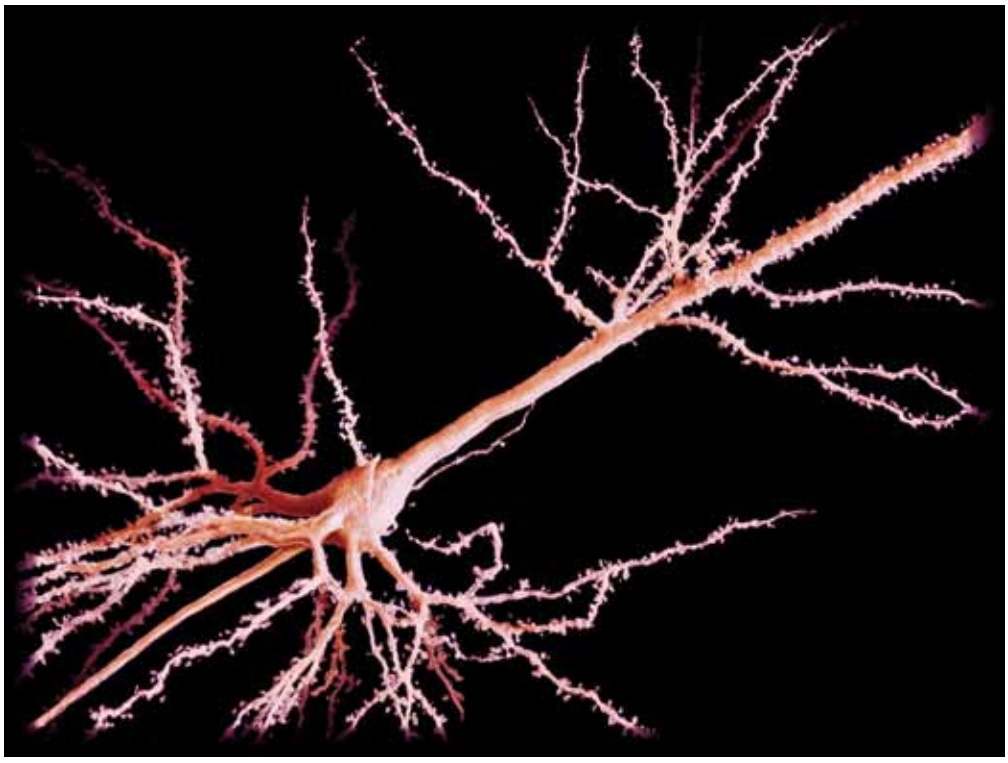
PHOTO ESSAY

3D Image of a Cortical Pyramidal Neuron



A pyramidal cell in the prefrontal cortex of the female rhesus monkey. The neuron was reconstructed by Mount Sinai neuroscientists and Anatomical Travelogue, a computer graphics team based in New York City, from thousands of high-magnification images in order to fully visualize the neuron's spines. These spines receive input from other neurons (i.e., synapses) that are critically important for cognition. Many of these spines are lost with aging, leading to cognitive decline.

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