

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.

This will be an exciting and important year for The Friedman Brain Institute (FBI), as we plan for the opening of Mount Sinai's Center for Science and Medicine (CSM) in the fourth quarter of 2012. The FBI will occupy two floors of the CSM, gaining 55,000 square feet of laboratory and office space. Along with recent faculty recruitments that will expand Mount Sinai's world-class neuroscience research and clinical community by one-third, we are nearing our goal of building the FBI into one of the nation's foremost brain-science institutes.

A major focus of the FBI is the study of cognition, and the abnormalities that characterize most common brain disorders: Alzheimer's disease and other dementias, for example; Parkinson's disease; schizophrenia; autism; and depression. Understanding the neurobiological basis of cognition, both in health and disease, has long been a strength of Mount Sinai's neuroscience community and is a key focus of our current recruitment efforts.

We are currently building a "vertically integrated" research and clinical program to enable our scientists to identify the genes in humans that help determine an individual's normal cognitive

capacity or risk for disease. This knowledge can be further explored at detailed molecular, cellular, and circuit levels in animal models ranging from rodents to nonhuman primates. The goal is to have the novel insights they gain translated to the clinic: to better understand how the brain "thinks" and to develop new ways of intervening to maintain maximal function despite illness or aging.

This issue spotlights the exciting translational work in the neurobiology of cognition, particularly that associated with age-related memory decline, by two Mount Sinai neuroscientists, John H. Morrison, PhD, and Mark G. Baxter, PhD. Dr. Morrison is the Dean of Basic Sciences and of the Graduate School of Biological Sciences, the W.T.C. Johnson Professor of Geriatrics and Adult Development (Neurobiology of Aging), and Professor of Neuroscience. Dr. Baxter is Associate Professor of Neuroscience, Anesthesiology, and Geriatrics and Palliative Medicine.

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RESEARCH FRONTIERS

Synaptic Decline: Cause of Cognitive Impairment with Normal Aging

For many years, neuroscientists believed that the cognitive problems that often occur with normal aging resulted from the death of neurons, albeit involving much less neuron death than what occurs in Alzheimer's disease and other dementias. We now know that neuron death is minimal in the absence of a neurodegenerative disease. So, what is the neurobiological basis of age-related cognitive decline if it is not the loss of neurons?

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Multiple high resolution ($0.1 \mu \times 0.1 \mu \times 0.1 \mu$) z-stack tiles using a Zeiss 710 confocal laser scanning microscope of a lucifer-yellow iontophoretically filled prefrontal cortical neuron of a nonhuman primate, reconstructed using software applications developed by TheVisualMD, providing the most accurate, quantitative 3D depiction of a neuron

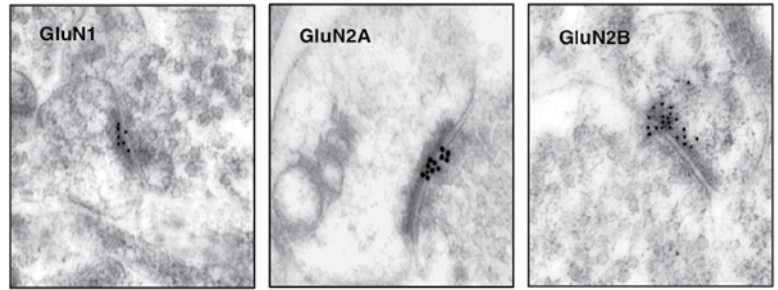
John H. Morrison, PhD, Dean of Basic Sciences and of the Graduate School of Biological Sciences, has been studying the neurobiological basis of cognitive aging for more than two decades.

Over the last 10 years, Dr. Morrison and his colleagues have revealed key age-related synaptic alterations that lead to cognitive decline. These studies have been carried out with high-powered quantitative approaches that were developed by Dr. Morrison, Patrick R. Hof, MD, the Regenstreif Professor and Vice Chair of the Department of Neuroscience, and the late Susan L. Wearne, PhD, Associate Professor of Neuroscience. These groundbreaking approaches enabled the quantification of molecular attributes of key synapses through high-resolution electron microscopic techniques, as well as quantification of dendritic arborizations, spine number, and spine size and morphology classifications through reconstructing individual neurons in 3D.

These techniques have been particularly valuable in revealing the synaptic correlates of cognitive performance and age-related cognitive decline when applied to young and aged nonhuman primates that have undergone extensive cognitive assessment. The hippocampus and prefrontal cortex are known to be particularly vulnerable to aging, with hippocampal alterations likely underlying defects in episodic and spatial memory, and prefrontal cortical changes leading to age-related declines in working memory and executive function.

Dr. Morrison's team has shown that in monkey prefrontal cortex, cognitive decline is associated with the loss of a select class of highly plastic excitatory synapses that utilizes glutamate as their neurotransmitter or chemical messenger and reside on small, thin dendritic spines. In comparison, the class of excitatory synapses that mediates highly stable circuits—associated with mushroom-shaped spines—are resistant to age-related changes. Close to 50 percent of the thin, plastic spines are lost with normal aging in prefrontal cortex, and the degree of such loss correlates directly with cognitive decline. These findings suggest that the unique cognitive domains of prefrontal cortex that are vulnerable to aging are highly dependent on the availability of highly plastic synapses that can be modified in the context of learning.

The pattern of synaptic aging and the synaptic correlates of performance in hippocampus are quite different from those observed in prefrontal cortex. There is minimal synapse loss in most regions of hippocampus with normal aging, although Dr. Morrison's research team has shown that a highly stable subclass of synapses is impaired with aging, and that this drives decline in cognitive tasks that rely on hippocampus, such as memory of places and events. There appears to be age-related alterations in the molecular plasticity of these hippocampal



Electron microscopic visualization of NMDA receptors, a type of glutamate receptor, at synapses in prefrontal cortex. GluN1 (left) is the obligatory subunit that forms receptor complexes with GluN2A (middle) and GluN2B (right). Note the tight distribution of the black gold particles in the vicinity of the dark postsynaptic density (PSD) within the dendritic spine. This technique provides highly quantitative information on the molecular profile of synapses that are affected by age and can be correlated with cognitive tasks.

synapses, rather than the compromised structural plasticity that drives decline in prefrontal cortex. Current research is focused on better understanding the nature of these molecular abnormalities.

Significantly, the same class of highly plastic synapses in prefrontal cortex that is vulnerable to aging, those associated with small, thin dendritic spines, is protected by estrogen treatment, and estrogen protects against age-related decline in cognitive tasks mediated by prefrontal cortex, as well. These observations suggest that while endocrine senescence may be linked to synaptic and cognitive aging, protection against age-related decline may be feasible, and that these synapses could be targeted for protection in humans, prior to onset of the very different neurodegenerative cascade that results in the disastrous cognitive decline that occurs in dementia.

Research currently being conducted at Mount Sinai takes such discoveries in animal models and uses them to develop new approaches to reduce the cognitive decline seen with aging with the goal of promoting successful aging in humans.



John H. Morrison, PhD

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Patrick R. Hof, MD, Named Editor of Journal

Patrick R. Hof, MD, the Regenstreif Professor and Vice Chair of the Department of Neuroscience, and Professor of Ophthalmology, and of Geriatrics and Palliative Care, was appointed Editor-in-Chief of *The Journal of Comparative Neurology*, effective January 1, 2012. The publication is the oldest continuously published journal of neuroscience, founded in 1891 by C.L. Herrick, PhD. Previous Editors-in-Chief include W. Maxwell Cowan, MD,

DPhil; Sanford L. Palay, MD; Clifford B. Saper, MD, PhD, Editor Emeritus; and Gerhardt von Bonin, MD.

Dr. Hof brings to the journal his expertise in brain evolution, human neuroanatomy and neuropathology, morphometry, and animal models of brain disease. The long tradition of scholarly work on comparative brain anatomy, in vertebrates and invertebrates, is a key feature of the journal, which Dr. Hof is committed to

maintain. At the same time, it will expand its coverage of structural and functional brain imaging in humans and animals, as well as other aspects of neuroscience. *The Journal of Comparative Neurology* will continue to provide the neuroscience community with a vehicle to publish definitive studies in systems neuroscience and maintain the essential and unique role that it has enjoyed over its 121-year history.

Investigating the Neurobiology of Higher Cognitive Function

Mount Sinai's efforts in cognitive neuroscience took a major leap forward with the recruitment of Mark G. Baxter, PhD, Associate Professor of Neuroscience, who joined the faculty in 2010, from the University of Oxford in the United Kingdom, to found the Glickenhau Laboratory of Neuropsychology, established by a generous gift from Seth and Sarah Glickenhau, long-time benefactors of The Mount Sinai Medical Center.

The Baxter Laboratory studies the neurobiological basis of higher cognitive function. The team's broad research interests include studying the role of particular neuromodulators in different forms of learning and memory, the requirement of certain brain structures and circuits for specific kinds of memory encoding and retrieval, the neurobiology of age-related changes in memory and cognition, and the short- and long-term effects of general anesthesia on cognition. Ultimately, researchers aim to understand how and why particular neural structures are necessary for specific aspects of cognitive function, and to use this knowledge to devise novel strategies to improve cognition impaired by brain disorders.

Dr. Baxter and his colleagues recently published a study in *Nature Neuroscience* showing that the loss of the neuromodulator acetylcholine—an important chemical messenger in the brain—in the prefrontal cortex of monkeys severely impairs working memory, measured in this case by the ability to remember the location of a hidden reward for a few seconds. This impairment was remarkably specific, because the monkeys performed normally on other tests of cognitive functions that also depend on the prefrontal cortex, such as the ability to apply complex behavioral strategies to solve a reward-gathering task, and the ability to adjust choice behavior in response to a change in the value of the goals.

These findings make two key contributions to understanding how acetylcholine is involved in functions of the prefrontal cortex. First, acetylcholine regulates neural mechanisms within the prefrontal cortex that are specific to working memory. Secondly, in brain diseases such as Alzheimer's disease, where acetylcholine is lost due to death of cholinergic neurons, the impairments that are seen in frontal lobe function are not, predominantly, the result of a loss of acetylcholine. This means that working-memory tasks may be particularly useful for determining effectiveness of drugs that improve cognition by mimicking acetylcholine's actions in the brain. (Three of the four drugs approved by the U.S. Food and Drug Administration for Alzheimer's disease act by increasing brain acetylcholine levels, based on discoveries made in large part by Mount Sinai's scientists decades ago.) However, because acetylcholine is not required for many cognitive functions of prefrontal cortex, other treatment strategies will be necessary to improve cognition outside of the domain of working memory.

The Baxter Laboratory is studying whether different kinds of working memory that require the prefrontal cortex—for example, working memory for objects rather than locations—also require acetylcholine, and whether working memory impairments after a loss of acetylcholine are associated with a disengagement of the prefrontal cortex from brain networks that are implicated in working-memory function.

The Baxter Laboratory is in a unique position to bridge basic research in simpler systems, where it is easier to investigate molecular mechanisms that support memory, to complex nervous systems

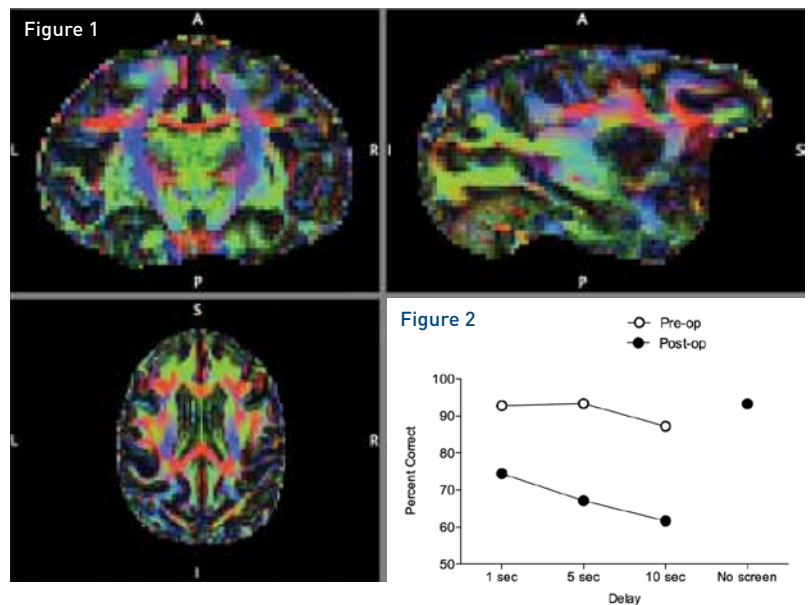


Figure 1. Diffusion imaging scan, a form of magnetic resonance imaging (MRI), of a rhesus monkey with a bilateral lesion of the hippocampus, a structure critical for normal memory function. The colors indicate the direction of diffusion, illustrating the flow of water molecules along white matter pathways in the brain. Red indicates left to right; blue, top to bottom; and green, front to back.

Figure 2. Working memory performance before (preop) and after (postop) removal of acetylcholine from the prefrontal cortex of rhesus monkeys. Working memory is dramatically impaired when acetylcholine is absent, but monkeys perform normally when there is no memory demand ("no screen" condition).

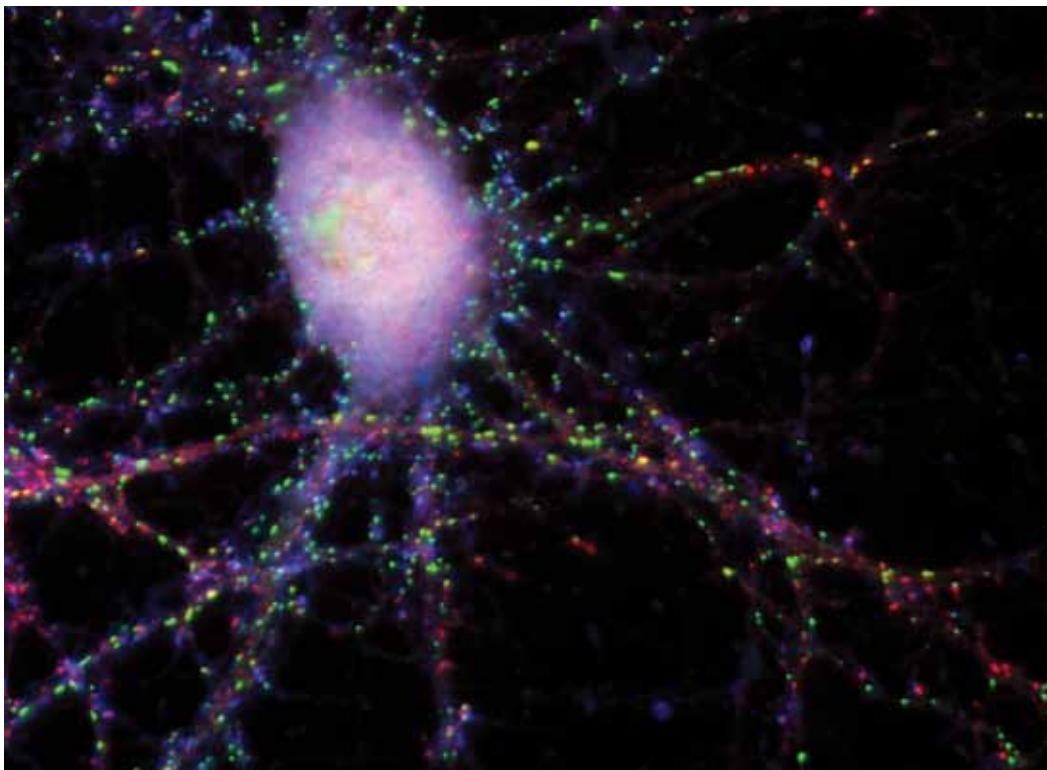
that closely resemble those of humans. By integrating sophisticated cognitive, neuroimaging, and neuroanatomical techniques to study the brain at multiple levels of organization, and through collaborations with Mount Sinai's other leading neuroscience laboratories, Dr. Baxter and his team have the ability to potentially uncover how complex brain systems give rise to high-level cognitive abilities, pointing toward strategies for repair and treatment of impaired cognition in disease.

Mark G. Baxter, PhD

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PHOTO ESSAY

Organization of Information Inflow onto a Single Neuron



Excitatory and inhibitory synapses decorate a mature hippocampal neuron grown in culture. Blue shows excitatory presynaptic nerve terminals labeled with an antibody against the vesicular glutamate transporter; red, the excitatory postsynaptic sites labeled with an antibody against postsynaptic density protein-95 (PSD95); and green, inhibitory postsynaptic sites labeled with an antibody against gephyrin.

Image by Tonya Anderson, PhD, Postdoctoral Fellow in Psychiatry, from the laboratory of Deanna L. Benson, PhD, Professor of Neuroscience



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