

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, by far, the most complex in the body, by orders of magnitude, which is why progress has lagged behind that of other medical specialties. However, for the first time, we now have the cellular and molecular tools that will begin to spark transformational advances in our understanding of the brain and spinal cord under normal and diseased conditions. We are thus poised over the next decade for truly revolutionary advances in neurology and psychiatry.

The Friedman Brain Institute (FBI) at The Mount Sinai Medical Center has a unique opportunity to play a leading role—nationally and internationally—in driving these advances. Our research and clinical work across the neurosciences is already very strong. As just one example, National Institutes of Health funding for our Department of Neuroscience is ranked fourth in the country. Now, with the construction of the Center for Science and Medicine, which will be completed in mid-2012, the FBI is in the midst

of a major recruitment effort to strengthen still further our research and clinical efforts. This is an enormous undertaking made possible by philanthropic support. We have already recruited approximately 20 new scientists and clinical leaders to the FBI's basic and clinical departments, and over the next several years, we will be adding about 30 faculty. This once-in-a-generation opportunity to build translational programs in the neurosciences will reinforce the FBI's position as one of the world's premier brain research institutions.

This issue highlights two of our recent recruits, Graham Ellis-Davies, PhD, Professor of Neuroscience, and Pamela Sklar, MD, PhD, Professor of Psychiatry, whose research complements existing strengths at Mount Sinai, driving our innovative approaches to brain and spinal cord disorders.

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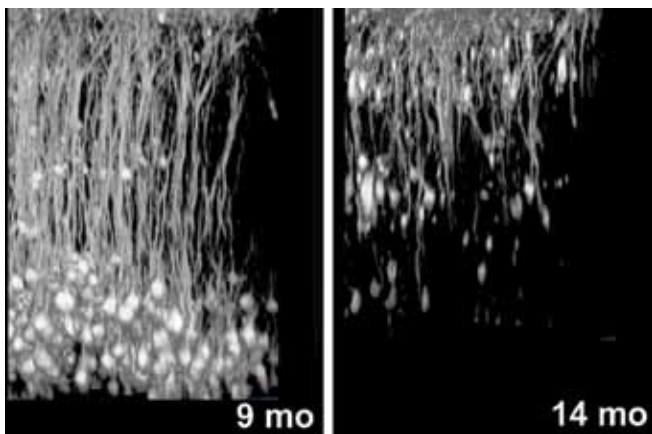


Figure 1. Two-photon microscopy images of cortical neurons in the same mouse. The first is at nine months of age, and the second, at 14 months, tracks the death of those neurons. **PREPARED BY SARAH CROWE, GRADUATE STUDENT IN THE ELLIS-DAVIES LABORATORY**

MEDICAL MILESTONES

Windows into the Brain: Novel Insight for Alzheimer's Disease

A human brain contains on the order of 100 billion nerve cells (or neurons), and each neuron forms thousands of connections, called synapses, with other neurons. Understanding how the brain functions requires an understanding of how individual synapses function in living brain tissue.

Graham Ellis-Davies, PhD, Professor of Neuroscience, and a recent recruit to the new Glickenhau Neuroscience Laboratories at Mount Sinai, uses a combination of advanced organic chemistry, laser physics (called two-photon laser scanning microscopy), and transgenic mice to investigate the structure and function of individual neurons and synapses in living mice.

A major target of this research is Alzheimer's disease. The Ellis-Davies lab uses transgenic mice that contain several genes that predispose humans to

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The Friedman Brain Institute External Advisory Committee

The first meeting of the FBI's External Advisory Committee was held in November and was a great success. The committee, composed of outstanding neuroscientists from around the United States, will provide crucial advice and guidance over the next several years as the FBI further develops its translational research and clinical programs in brain and spinal cord disorders.

Steven Hyman, MD (Chair)

Provost
Professor of Neurobiology
Harvard University

Carol Barnes, PhD

Regents' Professor of Psychology and Neurology
Director, Evelyn F. McKnight Brain Institute
University of Arizona

John Gabrieli, PhD

Grover Hermann Professor in
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Fred Gage, PhD

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Corey Goodman, PhD

Managing Director and co-founder of venBio LLC
Adjunct Professor
University of California, San Francisco

Larry Swanson, PhD

Milo Don and Lucille Appleman Professor
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University of Southern California

Stephen Warren, PhD

William Patterson Timmie Professor of
Human Genetics
Chair, Department of Human Genetics
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Windows into the Brain: Novel Insight for Alzheimer's Disease, *continued from page 1*

Alzheimer's disease. These mice have been combined with other mice whose neurons are labeled with a brightly fluorescing protein. Using sophisticated lasers, the lab can literally see into the brain of such mice and take pictures of the same labeled neurons over time as an Alzheimer's disease-like syndrome progresses. This method is so sensitive that the investigators can identify not only individual nerve cells but single synapses on those cells.

This approach is making it possible, for the first time, to image the enormous devastation that the brain suffers in Alzheimer's disease, and determine which specific part of a neuron dies first during the advent of the illness. For example, Dr. Ellis-Davies and colleagues have documented the dramatic death of neurons in the mouse cerebral cortex (the part of the brain crucial for learning and memory) that occurs between 9 and 14 months of age (*see Figure 1, page 1*). More recent studies of younger mice (3-5 months old) have revealed that the first physical sign of neuronal injury occurs in axons (types of long projections from neurons) located in deep cortical layers, with other parts of the neurons remaining healthy. Each axon lesion is intimately associated with an amyloid plaque. These discoveries now make it possible to image whether it is the amyloid plaque that initially attacks the neuron, or if the plaques are a by-product of neuronal degeneration.

The therapeutic implications of this work are profound. This new mouse model is being used to screen potential new treatments for Alzheimer's disease. The goal is to identify novel drugs that stop

progression of the illness, or even reverse its deadly course, in real time by using time-lapse movies over many months.

While this highlights the ways in which the Ellis-Davies lab uses light in highly innovative ways to image nerve cells, another key dimension of this work is the development of photosensitive molecules, called caged compounds, that are activated by brief flashes of light and release a smaller molecule. The Ellis-Davies lab has played a leading role worldwide in synthesizing "caged neurotransmitters," which enable tightly focused laser beams to activate neurotransmitters at single synapses on neurons in a way that precisely mimics normal biology (*see Figure 2, below*). Applying this method to the Alzheimer's mice will allow an even more penetrating look at the diseased brain.

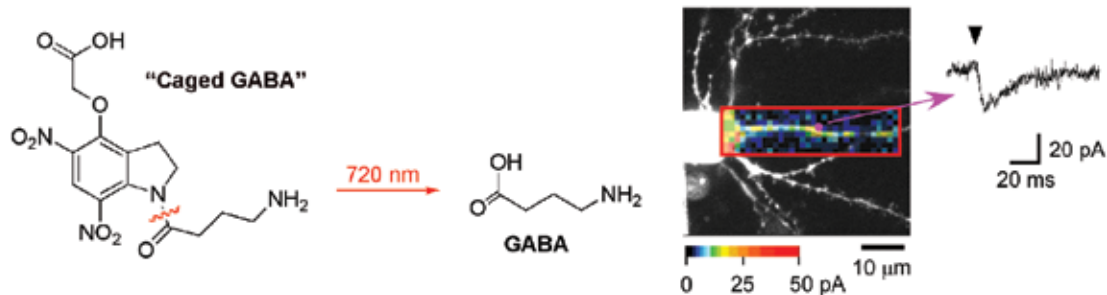
The great 19th century architect Louis Sullivan said that "form ever follows function." Using a combination of state-of-the-art technologies, Dr. Ellis-Davies and his team are leading the FBI's efforts to understand how the structure of neurons relates to their complex functional properties in health and disease.



Graham Ellis-Davies, PhD

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Figure 2. A caged version of the neurotransmitter GABA can be activated by two-photon excitation to evoke small, fast GABA currents to allow functional mapping of GABA receptor distribution in living brain tissue with single-synapse resolution.



Finding the Genetic Causes of Mental Illness

The diagnosis of virtually all psychiatric disorders, including autism, schizophrenia, and bipolar disorder, is still based solely on clinical symptoms, with very little biological understanding or insight into treatment. New technologies that enable the sequencing of millions of genetic markers in a cost-effective manner in thousands of individuals have created a revolution in medical genetics. These advances herald a new era for psychiatry, where individuals at risk will be diagnosed early on, and receive more effective treatments and ultimately preventive care.

In studies involving more than 10,000 individuals with schizophrenia, Pamela Sklar, MD, PhD, a recent recruit to Mount Sinai, and her colleagues at the International Schizophrenia Consortium, which she heads, have shown that an important source of risk for schizophrenia is having genes that are either duplicated or eliminated, so-called “copy number variations” or CNVs. Moreover, the team found that large numbers of genetic markers can be used as a composite measure of genetic risk, consistent with the realization that most forms of schizophrenia are caused by numerous genes even within a given individual. While this work is still in its early stages, one can imagine a scenario where a college student is seen in an emergency room with thought disturbances. For a modest cost, the genetic risk for schizophrenia could be evaluated and preventive treatments started as early as possible. Dr. Sklar is now furthering these groundbreaking studies at Mount Sinai as Professor of Psychiatry and Director of the new Division of Psychiatric Genomics.

The genetic basis of autism, like schizophrenia, is complicated, with perhaps hundreds of genes potentially involved, including CNVs (see Figure 1). Early diagnosis and treatment are particularly critical for autism, because early behavioral intervention has been shown to dramatically improve a child’s long-term prognosis. Again, imagine a 12-month-old child, where the parent and pediatrician have concerns, and where a genetic assessment suggests increased risk for autism. The genetic test, along with behavioral assessments, could support intensive behavioral intervention for the child that would otherwise be deferred because of cost. This scenario holds true promise for reducing the disability associated with autism.

The identification of genes that predispose individuals for schizophrenia, autism, or other psychiatric disorders, is also driving the search for novel therapies. Identification of such genes makes it possible for the first time to develop an animal model of the disorders. Researchers are now examining how these gene mutations alter brain function, thereby revealing novel protein targets for new therapies. The goal is to test drugs in the animal models, and, if promising, study them in clinical trials. As one example, Dr. Sklar’s research has identified genes involved in calcium channel activity, or in the actin cytoskeleton, as being important in many cases of bipolar disorder, work that is now suggesting novel approaches to treatment.

As another example, the laboratory of Joseph D. Buxbaum, PhD, the G. Harold and Leila Y. Mathers Professor of Psychiatry and

Neuroscience, Director of the Seaver Autism Center, and Chief of the FBI’s Center of Excellence on Neurodevelopmental Disorders, recently developed mice with an autism-causing mutation in the SHANK3 gene, which controls glutamate function in the brain. These SHANK3 mice exhibit impaired synaptic plasticity, consistent with learning deficits, and are pointing to new ways to reverse these abnormalities.

While this research is still at relatively early stages, genetic advances in psychiatry are at long last opening up a path toward transformational advances in the diagnosis and treatment of mental illness in our lifetime.

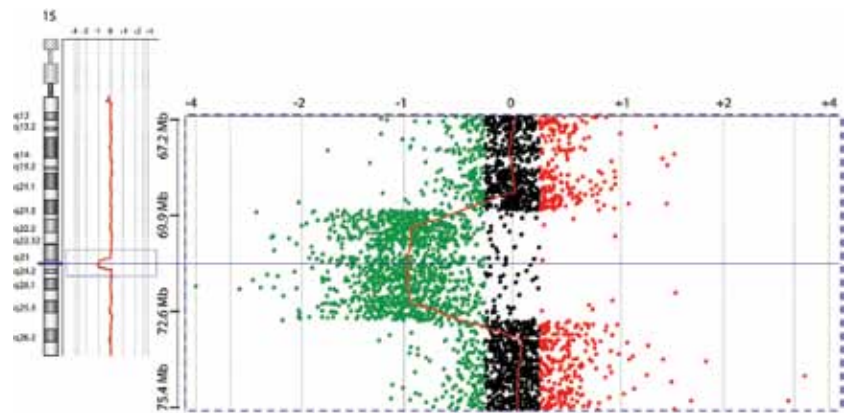


Figure 1. Human chromosome 15 (left side of figure) illustrating the hunt for disease-causing mutations. The red line shows the average of many thousands of measures and is at zero when there are normal DNA levels, and at 1 when half of the DNA (that from the mother or father) is missing. The missing DNA segment shown in the figure, a type of mutation, leads to autism in this patient. **IMAGE FROM THE BUXBAUM LAB**



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**New Autism Journal
 Founded by Scientist
 at The Friedman
 Brain Institute**

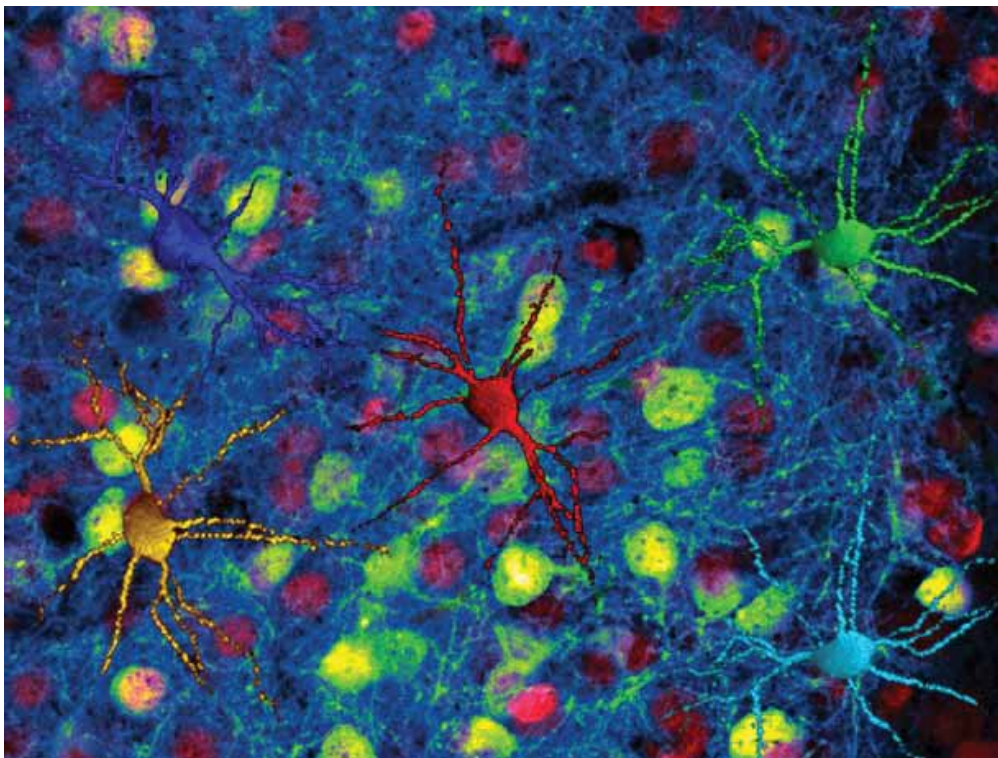
Molecular Autism is a new peer-reviewed, online-access journal that publishes basic, translational, and clinical research into the molecular basis of autism and related neurodevelopmental disorders. One of the founding and current editors-in-chief is

Joseph Buxbaum, PhD, who heads Mount Sinai’s FBI’s Center of Excellence on Neurodevelopmental Disorders.



PHOTO ESSAY

Brain Reward Neurons in 3D



The background is an immunohistochemical stain of cells expressing β -galactosidase (red) under the control of an NF κ B promoter, and medium spiny neurons expressing green fluorescent protein under control of the dopamine D2 receptor promoter (green) in the nucleus accumbens, a brain region important for reward, motivation, and mood. Yellow denotes cells positive for both stains. In the foreground are 3D reconstructions of Lucifer yellow-filled nucleus accumbens neurons as artistically rendered by the authors.

IMAGE FROM A RECENT COVER OF *THE JOURNAL OF NEUROSCIENCE*, WITH PERMISSION.



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