Mount Sinai

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The Brain Issue

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Susan B. Bressman, MD, Receives Top Honor

Susan B. Bressman, MD, a leading researcher, clinician, and educator in movement disorders and neurological conditions, has been named a "National Physician of the Year" for clinical excellence by Castle Connolly Medical Ltd., publisher of the annual *America's Top Doctors*® guides. Dr. Bressman is Chair of the Mirken Department of Neurology at Mount Sinai Beth Israel and Chair of Neurology at Mount Sinai Roosevelt and Mount Sinai St. Luke's.

An expert in Parkinson's disease, dystonia, and essential tremor, Dr. Bressman is credited with identifying four genes for dystonia, which is characterized by muscle contractions that cause twisting and repetitive motions or abnormal postures. In 2006, she and her colleagues at Albert Einstein College of Medicine reported that a specific gene mutation is a major cause of Parkinson's disease among Jews of Central and Eastern European descent. The results of their research were published that year in *The New England Journal of Medicine*.

Castle Connolly selected seven award recipients from among thousands of nominations that were submitted by physicians and

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Susan B. Bressman, MD

New Discoveries Shed Light on Schizophrenia

Rare mutations in specific sets of genes may increase one's chances of developing schizophrenia, according to investigators at Icahn School of Medicine at Mount Sinai, who recently led one of the largest and most comprehensive exome-sequencing studies of the psychiatric illness.

Lead investigators Pamela Sklar, MD, PhD, and Shaun Purcell, PhD

The findings, documented in two studies in the January 22, 2014, online issue of *Nature*, are helping researchers piece together the complex genetic architecture involved in schizophrenia, a chronic, debilitating illness that affects approximately 1 percent of the world's population, including 2.4 million Americans. The studies showed that some of the same genes implicated in schizophrenia also are associated with autism and intellectual disability.

"Many different DNA changes, some rare and some common in the population, affect a person's risk of developing schizophrenia," says Pamela Sklar, MD, PhD, Chief of the Division of Psychiatric Genomics, and Professor of Psychiatry, Neuroscience, and Genetics and Genomic Sciences at Icahn School of Medicine at Mount Sinai, who was one of the lead investigators. "We are working through all of the kinds of changes and examining them,

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› New Discoveries Shed Light on Schizophrenia *(continued from page 1)*

so that we can understand the genetic risk factors that lead to schizophrenia."

Dr. Sklar and Shaun Purcell, PhD, the studies' co-lead investigator, who is Associate Professor of Psychiatry at Icahn School of Medicine, collaborated with researchers from major institutions around the world, including Sweden, the United Kingdom, Bulgaria, and the United States.

One of the studies sequenced all of the genes of 2,536 patients with schizophrenia and 2,543 controls, with DNA samples collected by researchers at the Karolinska Institute in Sweden. The other study performed exome sequencing on 623 "trios" from Bulgaria, comprised of patients with schizophrenia and their parents.

"This is the most comprehensive look at the rare coding variants involved in schizophrenia to date," says Dr. Purcell. "The sheer volume of data generated in these projects is remarkable and the findings suggest new ways of thinking about the role of rare mutations in schizophrenia, given the large number of genes implicated and the synaptic biology to which they point."

Over the years, limited accessibility to the brain has made the organ uniquely difficult to study. With little direct information about brain tissue, and no available blood tests, schizophrenia and other mental illnesses are diagnosed solely by examining the patient's behavior.

The studies represent the first of many more steps that will be needed to truly understand the illness. Down the line, says Dr. Sklar, the researchers will examine what drives the mutations and why some lead to autism instead of schizophrenia. They will also use stem-cell technology to manipulate cells, and to see whether early interventions can improve a patient's prognosis.

"Despite the fact that we have known for decades that schizophrenia is highly heritable—with 65 percent to 80 percent of the risk being genetic—it has not been possible to identify individual genes that comprise that risk," says Eric J. Nestler, MD, PhD, Nash Family Professor of Neuroscience and Director of The Friedman Brain Institute at Mount Sinai. "These exciting new discoveries provide a path not only for a better understanding of the biological basis of schizophrenia, but also for developing fundamentally more effective ways of treating and, ultimately, preventing the illness."

Using Virtual-Reality Simulation to Improve Brain Surgery Outcomes

Virtual-reality simulation, designed to improve outcomes and reduce complications in patients undergoing brain surgery, is being pioneered at the Icahn School of Medicine at Mount Sinai as an innovative training tool for neurosurgery residents and as a program to help experienced surgeons advance their skill-sets.

The Brain Surgery Simulation Program, led by Joshua B. Bederson, MD, Professor and Chair of Neurosurgery at Mount Sinai, is using two simulators: the NeuroTouch Simulation System and Surgical Theater. Each has 3D software and handheld surgical controls to provide visual, touch, and sound feedback to the practitioner. A computer-generated "score" evaluates key measures, such as the amount of tumor removed, and the extent of bleeding and damage to healthy tissue. The Simulation Program team includes neurosurgeons, as well as neurologists, radiologists, residents, MD/PhD students, statisticians, and computational scientists.

Neurosurgical simulation will allow surgeons, who were previously unable to rehearse brain surgery using patient-specific data, to input brain images from a patient and information about comorbidities, create a 3D rendering of the patient's brain, and practice a procedure in advance of actual surgery, using the patient's virtual anatomy.

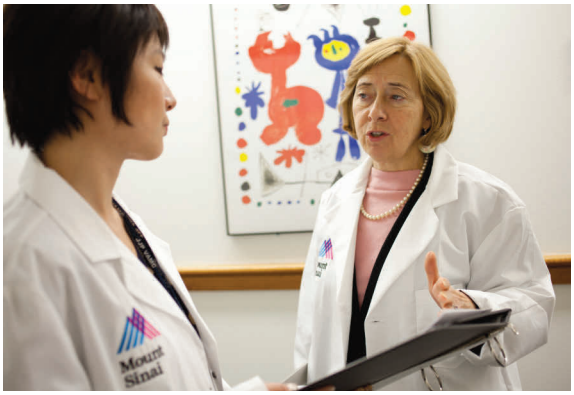
Joshua B. Bederson, MD, left, and Jonathan Rasouli, MD, PGY2, demonstrate the use of a neurosurgical simulation device.

"We believe that brain surgery simulation could potentially revolutionize the way we train and evaluate our surgeons," says Dr. Bederson. "By giving residents and faculty simulation training, as well as the opportunity to rehearse surgeries in the future, we expect to improve the safety of surgery and continue to advance the skills of our surgeons, in an effort to achieve better outcomes for our patients."

For more information, visit icahn.mssm.edu/brainsimulator

Studying the Effect of Vitamin E on Functional Decline in Alzheimer's Disease

Functional decline, measured as the loss of ability to accomplish activities of daily living, such as bathing and dressing, planning or cooking a meal, and paying bills, is the major symptom in individuals with Alzheimer's disease and the primary source of caregiver burden. Yet, few studies have focused on ways to slow this functional decline.



Mary Sano, PhD, right, with Amanda Burden, Senior Administrator for the Alzheimer's Disease Research Center at Icahn School of Medicine at Mount Sinai

In a recently published study in *The Journal of the American Medical Association*, researchers, co-led by an investigator from Icahn School of Medicine at Mount Sinai, reported that vitamin E, also known as alpha tocopherol, reduced functional decline in patients with mild-to-moderate Alzheimer's disease.

The findings come from a clinical trial that involved several hundred participants at 14 Veterans Affairs medical centers across the country, who were also taking currently approved medications for Alzheimer's disease, and spanned up to four years in duration. The study also showed significantly fewer deaths in the vitamin E group.

"There has been little to offer patients with mild-to-moderate dementia since a new class of drugs was introduced in the 1990s," says Mary Sano, PhD, the trial's co-investigator. "This trial revealed that vitamin E delays progression of functional decline by 19 percent per year, which can translate to a 6.2-month benefit." Dr. Sano is Associate Dean for Clinical Research and Professor of Psychiatry at Icahn School of Medicine, Director of Mount Sinai's Alzheimer's Disease Research Center, and Director of Research at the James J. Peters VA Medical Center in the Bronx, New York. The findings were consistent with an earlier study led by Dr. Sano that revealed a similar delay in functional decline in moderately severe Alzheimer's patients. No added benefit in memory or cognition was seen in either study.

Specifically, researchers investigated the effectiveness of 2,000 IU daily of alpha tocopherol alone, and in combination with memantine, a commonly prescribed drug for Alzheimer's marketed as Namenda® and approved only for moderate-to-severe Alzheimer's disease. The study also evaluated memantine alone and a placebo. Only the group using alpha tocopherol experienced results of slower functional decline. It was the first large-scale clinical trial to assess not only the effectiveness of alpha tocopherol in patients with mild-to-moderate Alzheimer's disease, but also in combination with memantine.

"The delay in functional decline also translated to a reduction of an estimated two hours of caregiver time per day, which has the potential, after further research, to have a major effect on informal and direct medical care costs," says Dr. Sano. "Maintaining the ability to perform activities of daily living is very relevant to patients and to caregivers."

Susan B. Bressman, MD, Receives Top Honor *(continued from page 1)*

leaders of major medical centers, specialty hospitals, teaching hospitals, and regional and community medical centers throughout the United States. All nominees were reviewed and approved by Castle Connolly's Medical Advisory Board.

The award honors dedicated physicians whose skills have improved the lives of countless people throughout the world. Dr. Bressman will receive her award on Monday, March 31, at a special ceremony at The Pierre hotel in Manhattan.

"I am delighted to be honored by Castle Connolly's Medical Advisory Board for our research and for providing much-needed care to patients who are affected by movement disorders and turn to us for help," says Dr. Bressman. "Whatever successes we have achieved would not have been possible without the collective efforts of a dedicated team of neurologists, geneticists, surgeons, genetic counselors, psychiatrists, physical therapists, and other experts. We hope that our research efforts will lead to better treatments and ways to slow progression or prevent movement disorders."

Under her leadership, Mount Sinai Beth Israel has become one of the leading sites for the Michael J. Fox Foundation-sponsored international consortium, which studies the genetics of Parkinson's disease. The Department of Neurology also has one of only 39 National Parkinson Foundation Centers of Excellence. A frequent lecturer and advisor to national and international organizations, including the American Academy of Neurology, Dr. Bressman is also a highly regarded mentor who trains gifted young physicians.

"Dr. Bressman's award as National Physician of the Year honors her groundbreaking work in research and clinical care. We are pleased that Castle Connolly has recognized her profound devotion to her work, and her remarkable talents as an academic neurologist," says Stuart C. Sealfon, MD, Glickenhaus Professor, and Chairman of the Department of Neurology for the Mount Sinai Health System.

Second Annual Brain Awareness Fair

The public is invited to Icahn School of Medicine at Mount Sinai's Second Annual Brain Awareness Fair, a popular event offering educational hands-on activities and demonstrations for adults and children. The event will take place on Thursday, March 13, from 3:30 – 6:30 pm at The Mount Sinai Hospital campus, Annenberg West Lobby.

Adults can meet leading members of the Mount Sinai faculty to discuss topics such as addiction, Alzheimer's disease, autism, and mental health. They can learn how physicians use brain scans to diagnose disease, and take a memory test. Children can see real animal brains, examine human brain cells under a microscope, and enjoy a number of other hands-on experiences.

The Brain Fair is organized by the Sinai Neuroscience Outreach Program, which works closely with K-12 teachers in East Harlem public schools to develop neuroscience lessons that encourage critical thinking. It is being held during Brain Awareness Week, March 10 – 16, an international campaign supported by The Dana Foundation to promote brain awareness. Other Brain Awareness Week events are being held across New York City. To learn more, visit the braiNY website at www.comebebrainy.com.

The Brain Fair is supported by the Center for Excellence in Youth Education at Icahn School of Medicine at Mount Sinai, The Dana Foundation, The Friedman Brain Institute at Icahn School of Medicine at Mount Sinai, the Greater NYC Chapter of the Society for Neuroscience, and the Sinai Neuroscience Outreach Program.

The Art of the Brain

In honor of Brain Awareness Week, The Friedman Brain Institute will host an "Art of the Brain" exhibition of images that celebrates the beauty of the brain as seen through the eyes of some of the world's leading researchers. The images were created using advanced technology, allowing Mount Sinai scientists to better understand how the brain works and to accelerate the development of new treatments for brain disorders. To learn more about The Friedman Brain Institute, visit www.mountsinai.org/fbi.

Monday, March 10 – Sunday, March 16
The Mount Sinai Hospital Campus
Guggenheim Pavilion Atrium

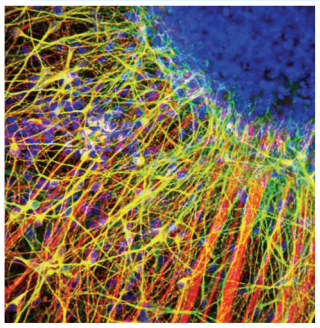


Image of neurons derived from a patient with schizophrenia at 400x magnification

Image courtesy of Kristen Brennand, PhD, Assistant Professor, Psychiatry, and Neuroscience

New Findings from Mount Sinai's Seaver Autism Center

The most recent study from the Seaver Autism Center at Mount Sinai draws a possible link between the genetic abnormalities attributed to autism spectrum disorder (ASD), and dysregulation of the mechanism by which unused neural connections are pruned during development. This information builds upon prior discoveries at the Seaver Center, which identified three kinds of genetic mutations that are believed to contribute to autism risk: *de novo* mutations; recessive or X-linked mutations; and small chromosomal abnormalities.

In other news, the Seaver Center is conducting a trial to determine whether insulin-like growth factor-1 (IGF-1) can serve as an effective treatment for ASD patients with mutations in the SHANK3 gene—one of the strongest genes for ASD. IGF-1, approved by the U.S. Food and Drug Administration, has been effective in reversing synaptic and motor deficits in SHANK3-deficient mouse and rat models. The Seaver Center is now planning to begin an additional trial to see whether IGF-1 is effective in ASD patients without SHANK3 deficiency.

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2014 Marketing & Communications
Carrie Gottlieb, *Editor*
Marilyn Balamaci, *Editor*
Ha Ly, *Graphics Manager*

SUBMISSIONS
Box 1475
inside@mssm.edu

VISIT INSIDE ON THE WEB
www.mountsinai.org/inside

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