THE PUBLICATION OF THE NEUROSCIENCES INSTITUTE

BRAINMATTERS

Fall/Winter 2009

NIRAJ DESAI: Striving to Understand Autism

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The Understanding of Use and the Use of Understanding

Science is imagination in the service of the verifiable truth. Its goal is to understand our place in nature. In the pursuit of that goal, it develops and applies technological advances. In recent years, there has been an explosion of technological progress in biological research. We can explore the human brain, for example, by non-invasive techniques such as functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). These resources allow us to better picture how the brain works in health and disease. But, as valuable as these applications are in the practical domain, we must not forget the goal of understanding how the human species arose during evolution. This grand panorama helps us to establish and realize human values, as well as to yield practical means of assuring mental and bodily health. Both understanding and practical applications are the abiding concerns of our scientists at The Neurosciences Institute.

Gerald M. Edelman, M.D., Ph.D.
Director

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NIRAJ DESAI: Striving to Understand Autism

In the world of brain-based disorders, one of the more heartbreaking for parents and challenging for scientists is the spectrum disorder known as autism. If the suffering that results from autism is to be eliminated at some point in the future, it may well be through the work of a researcher like Niraj S. Desai, Ph.D., Associate Fellow in Experimental Neurobiology at The Neurosciences Institute.

Desai, in his study of the mammalian neocortex, is driven by a growing sense that his work not only will lead to a groundbreaking understanding of the underlying processes that cause autism, but quite possibly to the development of therapies to help mitigate and hopefully prevent the disorder.

While he cautions the latter may be some years down the road, Desai and his fellow researchers at the Institute believe they have made significant progress in creating a framework in rodent models for learning what changes might be occurring in the brain to cause the symptoms of autism. In humans, these symptoms include mental retardation, impaired language and communication skills, reduced social interactions, repetitive behaviors, and restricted interests.

"We're excited because we're making real progress in understanding the basic biology of how neural circuits develop and change early in mammalian development, whether it's at the level of the entire brain or down to a single neuron or molecule," Desai says. "What's equally fascinating and potentially crucial to developing future therapies is that we're also beginning to learn how these circuits are affected by prenatal or environmental influences that may lead to autism, including genetic defect, exposure to alcohol or certain chemicals, maternal fever, injury, or other possible triggers."

As often happens in research, by studying what can and does go wrong, Desai and his team have discovered some of the processes by which the brain's

Dr. Desai describes his work to Institute members at the Minding the Brain event

"I've always loved science because one of the primary motivations in my life has been to understand how things work."

flexibility actually keeps normal development intact in the face of perturbations described above.

"It's yet another confirmation that the nervous system is a great piece of 'engineering'," he says. "The plasticity in the neocortex is really amazing, especially since there are so many things that can go wrong during development. Yet we often see significant self-correction that seems to be built into the very structure of the neural circuits."

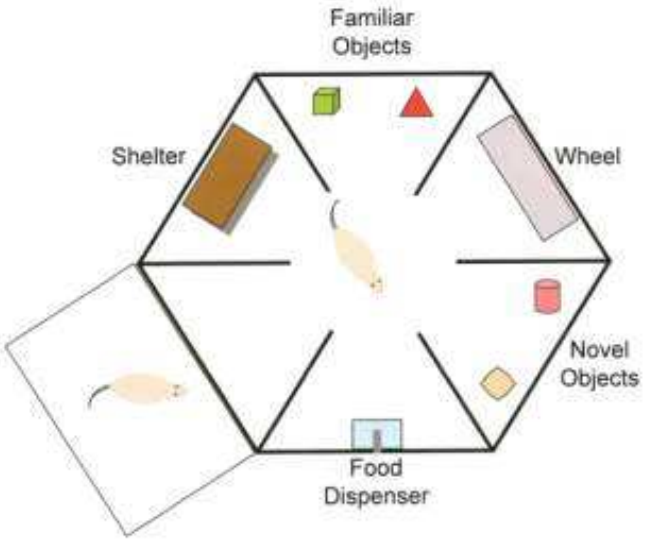
"We're not yet sure why and how this occurs, but we believe the manner in which each individual brain responds and adapts to these various influences may account for why there seems to be such a wide spectrum of autism disorders, ranging from those who are severely retarded and virtually non-functioning at one extreme all the way to those with Asperger's Syndrome who are high functioning and can lead relatively normal lives."

Desai's technique for studying these processes involves an analysis of rat behavior after prenatal treatment with valproic acid. Such rats often exhibit symptoms that make them a model for studies of autism. He places such a rat in a maze that allows the rat to choose to interact socially with another rat, as well as choose to engage with familiar objects or novel objects. The rat's behavior is videotaped and later analyzed to determine the level of autism-like behavior, which typically includes an aversion to social interaction and to novel items.

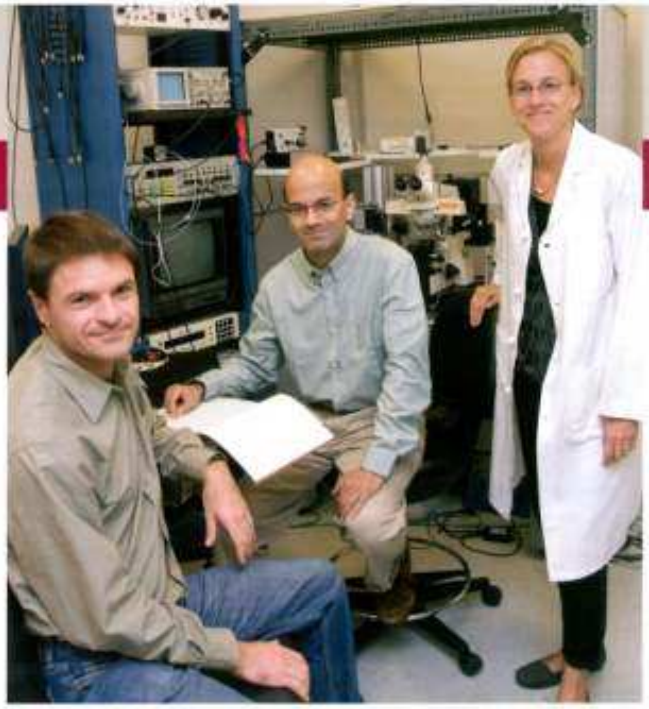
To analyze brain physiology, slices of the prefrontal cortex, an area thought to be connected to autistic behavior, are then taken from those with identifiable symptoms resembling those of autism. By examining the slices under a microscope at the neuronal level and comparing them with the corresponding cells of healthy rats, Desai is able to build a picture of autistic behavior at the cellular level, including how the cells have changed, how their firing properties may have been modified, and how their responses to synaptic input varies.

Observing Desai at work in his lab so deeply immersed in neurobiology, it is somewhat hard to believe that he didn't even enter the field until after he had earned a Ph.D. in physics at Cornell University in the mid 1990s. A couple of factors led him to leave the world of physics for biology.

At the time he was working on his doctorate, Desai believed there were deep and important problems in physics, but did not think he was personally well-positioned, through his thesis work, to address them. By contrast, he thought there were more compelling and more conveniently addressed problems



A rat with symptoms of autism interacts in a specially designed maze to be observed for social interaction and interest in novel objects. The six-chambered maze includes a running wheel, novel objects, a food dispenser, an unfamiliar rat, a covered shelter, and familiar objects.



Drs. Stephen Cowen, Niraj Desai and Elizabeth Walcott work together to better understand autism

available in biology. Those feelings were confirmed by a speech he attended by the famed Nobel Prize-winning physicist Hans Bethe.

"Bethe said he thought the 20th Century had been the century of physics with the advent of relativity and quantum mechanics. But he guessed that the 21st Century would be the century of biology because it was the field in which there was so much left to understand, and that the experimental and theoretical tools to really understand biological systems would finally be available. That was extremely influential in my decision."

Serendipitously, Desai saw an ad in *Science* magazine that seemed to be written just for him: the Sloan Center for Theoretical Neurobiology at Brandeis University was looking for post-doctoral fellows with a Ph.D. in physics or math, but with no biology experience required. Desai got the job and spent six years at the university becoming an expert on the plasticity of neural circuits. He then joined the staff at The Neurosciences Institute, a move he believes will be among the most important of his career.

"The Institute offers an excellent environment for my research," Desai says. "The work here is based on theoretical neurobiology and looking at the big picture, which is my main interest, but at the same time the research is based on a foundation of basic biological research that reveals the core principles of how the brain works, with the potential for practical application."

"Most important to me is the freedom I have here at the Institute to delve into unexplored areas I believe are important and to collaborate with my peers. Not only are there no barriers among researchers, but collaboration is strongly encouraged, allowing me to add the tremendous talents and resources of other scientists at the Institute to my own research, which in turn has enabled me to expand the scope and quality in ways I could never have achieved working alone."

"Most important to me is the freedom I have here at the Institute to delve into unexplored areas I believe are important and to collaborate with my peers."

Desai believes his time at the Institute has not only made him a better researcher, but also a more complete and caring scientist.

"I've always loved science because one of the primary motivations in my life has been to understand how things work," he says. "While that motivation remains and will always define who I am as a scientist, in recent years I've developed an accompanying driving force in my life, and that is to use my research to make a difference in people's lives. If I am fortunate enough that my work leads to some form of therapy to help those with autism or keeps the disorder from occurring in the first place, that would quite likely be the most gratifying accomplishment of my career."

GLOSSARY

Plasticity – the ability to change

Neuron – an excitable cell in the brain

Valproic Acid – chemical compound used to treat migraine and bipolar disorder, no longer prescribed to pregnant women

Physiology – study of the functions of living organisms

Prefrontal Cortex – brain region linked to planning complex cognitive behaviors

Synaptic – referring to signals between neurons

If we could talk to the animals...

Non-human research models provide our neuroscientists with complex living systems that can be studied across the levels of cells, tissues, organs, and behaviors. Animals can interact and react to stimuli, shedding light on how the brain works. Many animals are biologically similar to humans in many ways, yet simpler to study which makes them effective models for research at The Neurosciences Institute. Here are a few of our research projects that prominently feature non-human subjects.

SO YOU THINK YOU CAN DANCE!

Drs. Aniruddh Patel and John Iversen discovered Snowball, a cockatoo with more moves than Fred Astaire, on YouTube. This discovery opened the door to a new kind of rhythm research. Until their work was published in *Current Biology*, with Snowball appearing on the May 2009 cover, dancing or synchronizing movement with music was widely thought to be a uniquely human behavior. But Snowball most definitely has rhythm and moves with the beat of music even as the tempo is changed. More than being a curiosity, this finding has implications for the understanding and treatment of human movement disorders, such as Parkinson's disease, and could broaden our knowledge of human motor systems.

SHOO FLY, DON'T BOTHER ME

Why do we sleep? How do our brains regulate what we know to be an important human behavior? What are the connections between nutrition, sleep and appetite? For the answers to those questions we may look no further than that fruit fly hovering over our banana. Dr. Cynthia Hughes, recent recipient of a San Diego Foundation Blasker-Rose-Miah grant, uses *Drosophila melanogaster*, the common fruit fly, to explore her hypothesis that a particular set of neurons may play the role of "energy czar" in the brain by evaluating energy status and sending signals to control both appetite and sleep.

MINDING THE BRAIN EDUCATIONAL EVENT

The Institute opened its doors on Saturday, October 24, to its members, friends, and special guests for a taste of the variety of research being done at the Institute. Participants were able to customize their experience by selecting two presentations from the four offered by Drs. John Iversen, Cynthia Hughes, Niraj Desai, and David Edelman.

The event opened with the presentation "Of Time and Memory: Using Robots to Understand How We Store Personal Experience" by Dr. Jason Fleischer. Studying the neuronal activity in the hippocampus of rats has revealed important information in the areas of memory and navigation which guides our scientist's brain modeling and building of the Brain-Based Devices being developed at the Institute.

Following the presentations, guests enjoyed talking one-on-one with several of the Institute's scientists and Trustees at a reception on the rooftop terrace.

From top to bottom: Trustee Bill Gedale with Member Nancy Vaughan learn about the research work of Dr. Fred Jones of the Institute; Dr. David Edelman presents his work on animal consciousness; Dr. John Iversen answers questions about how his study of rhythm may help us understand more about movement disorders; at the rooftop reception, Dr. Cynthia Hughes draws a crowd "hungry" for more information about sleep and appetite; Dr. Jason Fleischer presents "Of Time and Memory" to open the day's program

COMMUNITY LECTURES

The Neurosciences Institute is committed to sharing our knowledge with the community. Throughout the year various presentations and lectures are presented to community groups and to Institute members, and feature highlights of the latest research projects.

GERALD M. EDELMAN, M.D., PH.D.
"Consciousness: How Matter Becomes Imagination"
September 15, 2009

In a collaborative effort with the San Diego Natural History Museum, The Neurosciences Institute presented an evening discussion of neuroscience with Dr. Edelman. In his presentation, Dr. Edelman discussed theories of how the brain works and how consciousness emerges during evolution.

DISCUSSING THE MIND AND ITS COMPLEXITIES

As a community service, Institute scientists deliver quarterly presentations about their latest research to the residents of Casa de Mañana in La Jolla. This series has become very popular with residents and members of the Institute, who are also invited.

Among the recent presentations include:

"How Scientists Study Disease: Animal Models of Autism" by Niraj Desai, Ph.D.
August 14, 2009

"Why Do Animals Need to Sleep?" by Joe Gally, Ph.D.
December 11, 2009

LIBRARY ROUNDTABLE LECTURE SERIES

The Neurosciences Institute presents its own community lecture series several times each year at no charge to the public. These lectures are delivered by leading figures in brain science and related fields.

IRENE PEPPERBERG, PH.D.
"Talking with Animals: Studies on the Cognitive and Communicative Abilities of Grey Parrots"
June 18, 2009

Dr. Pepperberg discussed her groundbreaking work with Alex, the African Grey Parrot. Alex exhibited math skills, developed his own "zero-like" concept, and was taught to vocalize numbers, suggesting that Grey parrots exhibit the potential for language, consciousness, and intelligence.

EBERHARD FETZ, PH.D.
"Interfacing Brains with Computers: Future Directions for Neuro-Prosthetics"
November 11, 2009

Dr. Fetz discussed his innovative work developing a small implantable computer chip, which provides artificial feedback that the brain can incorporate into its normal function. This research has numerous clinical applications for bridging damaged biological pathways.

COMING EVENTS AT THE INSTITUTE

JANUARY 31, 2010
San Diego Regional Brain Bee
A competition for high school students to test their knowledge of the brain. Visit www.sandiegobrainbee.org for more information.

MARCH 21, 2010
Teen Discovery Day
An open house for local junior high and high school students to experience the Institute's exciting science and learn about careers in science. Parents and teachers are encouraged to attend. Contact Debbie Honeycutt at honeycutt@nsi.edu.

Minding the Arts Gala Event

AUGUST 30, 2009

THE NEUROSCIENCES INSTITUTE'S PERFORMING ARTS PROGRAM – BY THE NUMBERS

Local Non-Profits Helped Since 1996: **108**
Concerts & Lectures Presented Each Year: **90**
San Diegans Who Attend: **20,000**
Program Cost: **$300,000**

MINDING THE ARTS GALA EVENT – BY THE NUMBERS

Special Supportive Sponsors: **9**
Mouth-watering Food and Beverage Purveyors: **12**
Something for Everyone Performances: **3**
Much Appreciated Funds Raised: **$86,250**
Guests Who Had Fun Supporting This Important Program: **169**

Audrey Geisel with Dr. Gerald Edelman

The Hutchins Consort

Event Chair Joani Nelson with guest Neil Marmor

The NOTEables

RB Swingtet

Minding the Arts

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BE A PART OF DISCOVERY!

Dear Friends of the Institute,

It is a great privilege to work at The Neurosciences Institute where every day our brilliant scientists work together to lay the foundation for understanding the remarkably complex brain. Our donors have the satisfaction of supporting important work that is, without a doubt, setting the stage for ground-breaking advances in the areas of learning and in the treatment of brain injuries and disease.

The course of science is unpredictable. We don't know how or when the next world-changing discovery will be achieved. Perhaps it will be through the revolutionary Brain-Based Devices the Institute has invented and uses to explore the brain in a way that is impossible in living creatures. Or maybe it will be found in the pioneering work of our scientists who have made dramatic discoveries about how the brain perceives music and rhythm with important implications for learning and language. What we do know is that among the projects being undertaken at the Institute, extraordinary results are being generated; and every day provides new promise.

Several of the Institute's donors have recently approached me with questions about which research areas are most in need of funding. So, as 2009 comes to an end and people are considering their final charitable contributions for the year, I thought it might be helpful to outline below some of the projects most in need of additional support.

Gifts of any size are deeply appreciated, and gifts of $5,000 or more will entitle the donor to meet with the researchers and receive a report on the progress of the sponsored research. Please contact me about specific naming opportunities for additional fellowships or programs. Thank you for considering The Neurosciences Institute among your charitable priorities.

Rachel A. Jonte, *Vice President for Institute Relations*
jonte@nsi.edu • (858) 626-2018

Rachel Jonte with trustee and donor Lewis Cullman

"Extraordinary results are being generated; and every day provides new promise."

PROGRAMS THAT WELCOME YOUR SUPPORT

BRAIN PLASTICITY

explores how flexible and adaptable the brain is in the face of a changing environment. Such plasticity constitutes the basis of learning and memory, underlies functional recovery from brain damage and disease, pertains to age-related cognitive decline, and provides a potential scientific basis for rejuvenating an aging brain.

DECISION MAKING

investigates the neurophysiology of brain areas involved in the cost-benefit analysis underlying decision making. This work will provide information on the principles involved in the neural mechanisms that determine our actions. Our findings may lead to therapeutic treatments for neural disorders that affect our ability to make decisions.

MUSIC AND THE BRAIN

explores the impact of music and rhythmic sounds on the brain. This has potential for development of novel therapies that may be beneficial in a wide range of maladies, from Parkinson's disease to reducing stress in neonatal babies.

SLEEP AND APPETITE

investigates the connection between these two essential functions to determine if they share a common regulatory mechanism. Sleep disorders and obesity are both common in our modern age and this research has potential implications for drug development.

THE PUBLICATION OF THE NEUROSCIENCES INSTITUTE

BrainMatters

Fall/Winter 2009

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DONOR PROFILE

BARBARA AND JOHN COSTANTINO

Dedicated individuals such as the Board of Trustees, members, donors, and volunteers who have given freely of their talent, time, and resources—many of them for decades—ensure that The Neurosciences Institute maintains its unique environment for scientific inquiry.

Barbara and John Costantino epitomize the commitment of this special group. The New York couple has made the Institute an important part of their lives for over two decades. Not only have they made significant financial contributions to support the research and introduced numerous donors to the Institute, John has also served as a board member through that entire period, currently serves as treasurer, and has advised the scientists on commercial applications of their work.

"Barbara and I are endlessly fascinated by the scientific monastery feel of the Institute and the amazing advances in neurobiology which that environment has fostered over the years," John says. "We love to bring others into that world because we believe the Institute's ambitious objective of understanding how the brain works is not only crucial to vastly expanding our knowledge of that incredibly complex organ, but ultimately will have a significant impact on improving the human condition."

John, who is Managing General Partner at NGN Capital with 30 years of experience in the private equity markets, first learned of the Institute when he was introduced to Founder and Director Dr. Gerald M. Edelman in the 1970s when John was Managing Tax Partner of the Touche Ross New York office. The two became business associates and friends, and Costantino was asked to join the board shortly after the Institute was founded.

"I'm an amateur astronomer who has always been intrigued with matters of science and medicine, so it was exciting for me to become involved with an organization that is truly delving into the next scientific frontier and conducting some of the most ambitious brain research. The Institute's attempt to explain the nature of consciousness and the creation of brain-based devices that learn from their environment are just two incredible examples of where they are really ahead of the rest of the scientific community."

The Costantinos, who have two grown children and two grandchildren, are extremely active in their community—Barbara works with the Cabrini Missions and John is a trustee emeritus and one of the most involved and honored alumni of Fordham University and Fordham Law School.

"We support a lot of causes, but we will always find time for The Neurosciences Institute," John says. "We feel like we're part of a very special family."