## Program Highlights

# SOCIAL NEUROSCIENCE LABORATORY:
## TOWARD A BETTER UNDERSTANDING OF AUTISM AND SCHIZOPHRENIA SPECTRUM DISORDERS

What is it about our brains that "hardwires" us to seek out interactions with other people and to take pleasure in forming social relationships and attachments, beginning in earliest infancy, and continuing throughout life?

These are qualities that seem so much a part of us that many of us take them for granted. But what happens during brain development that interferes with the development of sociability in individuals with autism or schizophrenia spectrum disorders? These are the questions that drive work in the laboratory of Edward S. ("Ted") Brodkin, MD, Assistant Professor of Psychiatry at University of Pennsylvania.

*from left to right:*
*Mary Calderone, Matthew Torre, Rhia Shah, Edward ("Ted") Brodkin, Andrew Fairless, Arati Sadalge Kreibich, Holly Dow*

Dr. Brodkin's fascination with the neurobiology of social behaviors dates to his Harvard undergraduate years, when he studied Harry Harlow's work. "Although Harlow did not work on autism or schizophrenia, studying his groundbreaking work on the development of attachment in infancy and childhood got me hooked on the field of social neuroscience in general," Dr. Brodkin says. During his Psychiatry residency at Yale, he began to treat adults with autism spectrum disorders (ASD).

"I found the issues these patients were dealing with uniquely compelling," Dr. Brodkin recalls. "The difficulties with social interactions that they faced were beyond the level of simply being shy or introverted. It was extremely difficult or impossible for many of them to engage in the important activities of life that require navigating a social environment, such as functioning in school or work, shopping for basic necessities, or forming new relationships, even if they were intellectually bright. This led to a great deal of hardship and suffering for both the patients themselves and their families. While there are treatments for some of the associated symptoms of ASD, there are not yet treatments that adequately help with the core social behavior symptoms. I felt motivated to better understand the biology of ASD so that we could better help these patients."

Dr. Brodkin also recognized that he could fashion a career in medicine combining basic neuroscience research with clinical care. "During medical school, I was lucky enough to meet and interact with people like Steve Hyman, Eric Nestler, and Eric Kandel, which made me realize that it was possible to be a psychiatrist, but also to do basic neuroscience research to better understand the fundamental neurobiological basis of behaviors and psychiatric disorders," says Dr. Brodkin.

With this goal in mind, he immersed himself in basic science work during two postdoctoral research fellowships immediately following his residency. He first studied basic neurobiology at Yale in the laboratory of Eric Nestler, MD, PhD and then genetics at Princeton in the laboratory of Lee Silver, PhD. In 2002, Dr. Brodkin joined the faculty in Penn's Department of Psychiatry.

At Penn, Dr. Brodkin established a laboratory focused on social neuroscience to investigate the neurobiology and genetics of social behavior disruptions associated with ASD and schizophrenia. It's a fertile area for investigation. As in ASD, social behavior impairments in schizophrenia are extremely disabling; the underlying neurobiology is poorly understood; and current treatments are largely ineffective. While there are fairly effective treatments for many of the so-called "positive" symptoms of

*Continued on page 4*

*Continued from page 3*

schizophrenia, such as hallucinations and delusions, available treatments are inadequate for treating the "negative" or deficit symptoms, such as lack of interest in social interaction. The long-term goal of Dr. Brodkin's work is to provide a neurobiological and pathophysiological foundation for new treatment approaches in both ASD and schizophrenia.

Dr. Brodkin's lab uses mouse models to analyze the neurobiological mechanisms of social behaviors relevant to ASD and schizophrenia. The challenge lies in developing etiologically valid animal models, i.e. models that show behavioral and brain traits that are attributable to the same genetic and/or environmental factors that cause the disorders. At a biological level, autism and schizophrenia are not each single diseases, but rather each comprises biologically heterogeneous groups of disorders. Because our understanding of the genetic and environmental causes of these disorders has been progressing more rapidly in recent years, developing etiologically valid mouse models is becoming possible. The mouse is used because it is the leading model organism for studying mammalian genetics and for developing mammalian models of human disease. "For virtually every human gene, there is a mouse counterpart, and vice versa," Dr. Brodkin says. "So, as we identify human disease genes, we can study them in mice, and can develop mouse models of the disease."

"Although it may be impossible to model all symptoms of ASD or schizophrenia, such as complex language or higher order cognitive impairments, there are certain basic behavioral components of the disorders, such as reduction in a primal form of sociability (reduced seeking of social interaction), that we can observe and measure quantitatively in animals," Dr. Brodkin says. "We study animal models to try to understand the underlying biology on a deeper level than would be possible in human studies alone. But this is done best in close collaboration with clinical investigators, to make sure that the basic research questions we are asking, and the answers we are getting, are as relevant as possible to human health. Ideally there is an ongoing, reciprocal interaction between clinical and basic researchers, and I really have that here at Penn, which makes it a special place."

Dr. Brodkin's lab has identified regions of the mouse genome linked with social behavior phenotypes. In genes within those genomic regions, his lab is studying the effects of sequence variants (alleles) on social behaviors. Dr. Brodkin identified a specific mouse strain, the BALB/cJ strain, that shows low levels of social interaction and other brain traits that may be relevant to ASD. In 2007, Dr. Brodkin secured a five-year grant from the National Institute of Mental Health for a study entitled the "Neurobiology of Sociability in a Mouse Model System Relevant to Autism," which is part of the NIMH's new program in the Social Neuroscience of Mental Health. The goal is to test the links among low sociability and various brain traits in BALB/cJ mice. He is also studying social behaviors in mice with mutations of genes that have been linked with ASD or schizophrenia. He is using these mouse models both to better understand underlying brain mechanisms, and to test novel pharmacologic treatment approaches.

> "I would say for psychiatric illnesses, and particularly for our understanding of social behaviors," Dr. Brodkin acknowledges, "we really are at a very early stage of our understanding. There's a long way to go, but working toward better understanding of these disorders will be fascinating and will pay off in much better care for patients."

"We are interested in either obtaining or making mice with mutations in those genes," Dr. Brodkin explains, "and trying to understand the chain of events that leads from particular gene mutations, to alterations in brain development and function, to social withdrawal. And, finally, we will use these models as systems in which to test out new treatments that would restore sociability. We are still at very early stages in this endeavor, partly because the genes and environmental factors that predispose certain individuals to ASD and schizophrenia are just starting to be identified. We are also continuing to develop and refine the tools necessary to best understand the relevant phenotypes in mouse models. But it is a very exciting time, and the field as a whole seems to be on the threshold of a great deal of progress."

Dr. Brodkin also plans to examine the role that environmental factors play in the genesis of social behav-

*Continued on page 5*

*Continued from page 4*

ior disruptions, work already underway in collaboration with Michal Elovitz, MD in the Penn Department of Obstetrics and Gynecology. "Dr. Elovitz has developed a mouse model of prenatal inflammation, which appears to be a risk factor for ASD, so together we are studying the effects of prenatal inflammation on brain development and social behavior development," he says. "We also plan to study the effects of gene-environment interactions on brain and social behavior development."

Dr. Brodkin's lab is part of the Department's initiative to better understand ASD, schizophrenia, and other neurodevelopmental disorders. It complements the work of the Adult Developmental Disorders Program, directed by Anthony L. Rostain, MD, MA, which treats these disorders and conducts clinical research seeking improved treatments. Dr. Brodkin is an attending psychiatrist in that program. Dr. Brodkin's lab research also complements the work of the Neuropsychiatry division, which is focused on schizophrenia and directed by Raquel Gur, MD.

Dr. Brodkin explains that caring for patients informs his research. "I enjoy working with patients with ASD, and doing so focuses my research questions. Many of these patients can describe their subjective experiences of social situations very articulately, which gives us important insight."

"One of the best aspects of being at Penn is the terrific, collaborative research environment here," Dr. Brodkin says. Within the Department of Psychiatry, key collaborators include Wade Berrettini, MD, PhD, who has been a mentor as well, Irwin Lucki, PhD, Raquel Gur, MD, PhD, Ruben Gur, PhD, Steven Siegel, MD, PhD, Chang-Gyu Hahn, MD, PhD, Gregory Carlson, PhD, Steven Arnold, MD, Konrad Talbot, PhD, Falk Lohoff, MD, David Mandell, ScD, Anthony Rostain, MD, MA, and Adrian Raine, PhD. In the School of Medicine, collaborators include Robert Schultz, PhD, a Professor in the Department of Pediatrics and Director of Center for Autism Research at Children's Hospital of Philadelphia (CHOP), who uses neuroimaging to identify specific brain structural and functional abnormalities in autism; Hakon Hakonarson, MD, PhD, who directs the Center for Applied Genomics at CHOP; Michal Elovitz, MD in Obstetrics and Gynecology, who studies prenatal environmental factors in autism; Maja Bucan, PhD in Genetics, who studies behavioral and psychiatric genetics; and Harish Poptani, PhD and Christos Davatzikos, PhD in Radiology, who contribute neuroimaging expertise. Dr. Brodkin also collaborates extensively with Ted Abel, PhD in the Department of Biology in the School of Arts and Sciences, Martha Farah, PhD and Seth Gillihan, PhD in the Department of Psychology, and Tracy Bale, PhD in the Department of Animal Biology in the School of Veterinary Medicine.

"I also want to highlight the work of the extremely bright and talented people in my lab, who deserve so much of the credit for our work, including Holly Dow, Geena Sankoorikal, Kristin Kaercher, Andrew Fairless (a Penn neuroscience graduate student), and Arati S. Kreibich, PhD (a postdoctoral researcher), as well as many Penn undergraduates who have made significant contributions," says Dr. Brodkin.

"Being at Penn has benefited me in a lot of ways," says Dr. Brodkin. "The Department of Psychiatry enables me to have this kind of career where I can combine patient care with basic research. This is not true of every Psychiatry department around the country. And the level of interaction that is possible between faculty members at the medical school and the other schools of the University makes Penn really special."

Dr. Brodkin understands the formidable research challenges that must be overcome to achieve an understanding of complex social behaviors relevant to ASD and schizophrenia, but he also recognizes the potential rewards. "As Lewis Thomas wrote, the better we understand the basic pathophysiological mechanisms of diseases, the more effective and affordable our efforts to treat the diseases can become. This is illustrated well by the progress made in treating and preventing many bacterial infectious diseases in the 20th century."

"I would say for psychiatric illnesses, and particularly for our understanding of social behaviors," Dr. Brodkin acknowledges, "we really are at a very early stage of our understanding. There's a long way to go, but working toward better understanding of these disorders will be fascinating and will pay off in much better care for patients."

The journey may be challenging and protracted, but if we have learned anything so far from Dr. Brodkin and his laboratory's approach to understanding the basic neurobiology of social behaviors, that is more a source of inspiration than frustration. ❖