

DEVELOPMENTAL NEUROSCIENCE

Annual Report July 1, 2006 - June 30, 2007

1. Highlights

The department continues having success in obtaining outside support for its research projects. New support from the NIH, the Sackler Foundation, the Gatsby Initiative at Columbia, and the CJ Foundation resulted in over \$1,500,000 of new direct support for the coming year.

There were many honors awarded to the staff this year. Among the most significant were Dr. Barr's election as President of the International Society for Developmental Psychobiology, Dr. Gingrich's election to American College of Neuropsychopharmacology, and his selection to become a member of the Simons Foundation Autism Research Scientific Group.

The Department also experienced great success in disseminating results from their studies with over 30 articles, reviews and chapters being published this year. Among these, Dr. Hofer's theoretical article in the Annals of the New York Academy of Sciences described a new evolutionary model for the role of adaptation in resilience and vulnerability to disease. Drs. Monk, Myers, Fifer and colleagues published evidence in Developmental Psychobiology that child temperament is correlated with physiological traits recorded much earlier, during fetal development. In work published in Neuron, Dr. Gingrich's group showed that hallucinogens require recruitment of specific serotonin receptor-mediated signaling pathways to mediate their effects on behavior. Finally, an important study published by Dr. Schechter and colleagues in Attachment and Human Development demonstrated how trauma experienced by caregivers can adversely affect young children's mental representation of themselves and others.

2. Staff

Michael Myers, PhD, Chief, Research Scientist VI
Gordon Barr, PhD, Research Scientist V
Susan Brunelli, PhD, Research Scientist IV
William Fifer, PhD, Research Scientist VI
Jay Gingrich, MD, PhD, Psychiatrist II
Myron A. Hofer, MD, Director, Research Scientist VIII
Catherine Monk, Ph.D., Assistant Professor of Clinical Psychology
(Primary Dept., Behavioral Medicine)
Jonathon Polan, MD, Research Associate
Daniel Schechter, MD, Research Associate
Harry Shair, PhD, Research Scientist VI
Martha Welch, MD, Assistant Clinical Professor
Christoph Wiedenmayer, PhD, Research Associate

3. Overview

Research in the Department of Developmental Neuroscience is focused on understanding processes involved in the development of behavior and fundamental relationships between

behavior and biology. There are twelve investigators in the department interested in understanding how natural events and stressful experiences interact with genetic mechanisms to shape the course of normal and abnormal development. This work is driven by the belief that the study of developmental processes provides important clues about the origins of a wide spectrum of clinical conditions. Ongoing studies use a variety of novel animal models to investigate the neurobiological substrates of attachment, separation anxiety, fear responses, and pain regulation. These models include targeted gene deletion of neurotransmitter receptors in mice, programming of early nutritional and other environmental experiences, and selective breeding for behavioral traits in infancy. Studies involving human subjects examine the role of pre- and post-natal experiences on fetal, infant, child, and maternal behavior and physiology. Work in the division continues to reveal networks of neurobiological and behavioral processes within the fetal and early postnatal maternal environments which regulate the course of development and can shape adult outcome and vulnerability to a number of clinical conditions. Research activities in the department are augmented by a postdoctoral training grant that has received continuous funding from the National Institute of Mental Health for over 35 years, and by the Sackler Institute for Developmental Psychobiology headed by Dr. Hofer.

4. Current Research

Research in this department covers a very wide range of topics related to brain and behavior development and vulnerability to disease. One of our goals is to determine as early as possible whether individuals are at risk for subsequent neurobehavioral disorders. One example of this is Dr. Myers' work in which profiles of gene expression from high density expression arrays are used to determine if a given infant was subjected to suboptimal growth environments during gestation. These studies dovetail with the investigations by Drs. Monk, Fifer and Myers in which physiological markers during both gestation and early postnatal life are linked to later life vulnerabilities. In conjunction with this line of investigation are new studies by Dr. Fifer, with Drs. Ismee Williams from Pediatric Cardiology and Dr. Bradley Peterson, director of the NYSPI MRI Lab, investigating the impact of congenital heart disease on fetal and neonatal neurologic structure, function and outcome.

Finally, in other work with human subjects Dr. Schechter is investigating how violence-related posttraumatic stress disorder (PTSD) subsequently affects the ways mothers think about and interact with their toddlers. This year, in collaboration with Dr. Peterson, he found that PTSD-afflicted mothers' exhibited significant differences from non-PTSD afflicted controls in terms of brain activity during the viewing of videotape clips of their own and unfamiliar children during stressful and non-stressful situations. These findings have added an important functional neuroanatomical dimension to Dr. Schechter's findings of group differences in maternal behavior in the lab and at home, self reported parenting stress, maternal autonomic system physiology, and child symptomatology.

In basic studies, Dr. Brunelli continues to investigate a novel animal model of infant anxiety. She is currently assessing how animals selectively bred for high levels of separation anxiety in infancy behave under conditions later in life that precipitate aggressive behavior, particularly the aggression associated with alcohol consumption. She also has documented genetic differences in

the expression of CNS genes involved in regulation of the HPA axis, genes responsive to cell damage, and genes involved in myelination and aging processes.

Working with Dr. Brunelli, Dr. Shair is investigating the neurobehavioral substrates underlying the *formation* of the earliest social bonds by rat pups. In particular, the research attempts to determine if the formation of attachment to the dam and to the sire are regulated by the same processes. This work overlaps with efforts by Dr. Polan which focuses on investigations of the earliest forms of maternal attachment in rodents by examining how these behaviors are expressed in genetically engineered mice with alterations in the expression of genes for the dopamine and glutamate neurotransmitters systems. In other studies with Drs. Muller, Myers, and Moore (Lieber Center), Dr. Shair is investigating the *expression* of infantile social behaviors. They have demonstrated that activation of the dopamine type 2 receptors in the nucleus accumbens inhibits distress vocalization of pups isolated directly from their dams, whereas the calming effect of the mother, but not siblings, involves dopamine receptor activation in other brain areas. To our knowledge, this research is the first that distinguishes between the neurochemical control of affiliative responses of pups to the dam and to littermates. This work is paralleled by Dr. Wiedenmayer's current research which is aimed at understanding how emotions are regulated in early ontogeny. He studies the role of the prefrontal cortex in fear in young rats. Interactions with the amygdala are examined at different ages to determine the function of the prefrontal cortex across development.

Dr. Barr continues to study how early experience alters later function by investigating the immediate effects of that experience on the infant and the long term effects in adults. The most recent projects have focused on the long term effects of tissue injury to understand consequences for premature infants, effects of axotomy induced by spinal cord injury (with J. Houlé and M. Murray), and on the paradoxical preference learning that occurs when an odor is paired with a mild shock as a model of early child abuse (with R. Sullivan). The first findings, using microarray gene expression, show an important role of dopamine in this unusual learning preference. Most recently, it was found that when the odor of alcohol is paired with shock, there are long-term changes in alcohol intake in the adult (with Sullivan and M.Lewis).

Work in Dr. Welch's laboratory examines the biological mechanisms of nurture and is exploring new treatments for developmental, behavioral disorders and inflammatory disorders. Funds from of the BrainGut Initiative, a collaborative project with Michael Gershon in the Department of Pathology and Cell Biology, is supporting new work testing the hypothesis that gastrointestinal inflammation and concomitant brain effects in acquired and congenital/genetic rodent models of colitis may be effectively treated with a combination of secretin and oxytocin. Additional new findings include demonstration of the oxytocin receptor in the enteric nervous system. Finally, a clinical initiative is being planned to investigate the effects of enhanced nurture on premature infants in collaboration with the neonatal intensive care unit at Babies' Hospital.

Dr. Hofer is overseeing the initiative funded by the Sackler Foundation which is focused on understanding how serotonin and serotonin receptors work during early development to shape brain function and behavior later in life. Building on work in Dr. Gingrich's laboratory, this multi-investigator program studies a broad range of topics including: the effects of treatment of maternal depression with SSRIs on fetal and newborn behavior, brain electrophysiology and

autonomic physiology, the alterations in brain development that occur in mice with deletion of the serotonin transporter gene, a model for patients at genetic risk for major depression, and the effects of SSRI exposure on rats during different prenatal periods on newborn and adolescent brain and behavior development.

The Gingrich laboratory is also focusing on the role of serotonin 2A receptors in modulating the special properties of hallucinogenic compounds. As mentioned previously, this work was the subject of a 2007 Neuron article by Dr. Gingrich and his laboratory. They found that LSD-like drugs act via 5-HT_{2A} receptors in the cortex to alter sensory processing and signal transduction in mice. This observation has important implications for the role of higher brain processes in the unusual properties of these agents. This study has led to the development of translational initiatives with Scientists at Mt. Sinai and Cornell campuses.

5. Education and Training

The department directs an NIMH-funded Research Training Program for postdoctoral fellows. This program supports the mental health related research of 5 M.D. and Ph.D. fellows. There are 23 sponsoring faculty members in the program that represent five other departments from the Psychiatric Institute and the Perinatology Division of the Pediatrics Department at Columbia. In addition, the department sponsors the training and research of several undergraduate and graduate students, as well as postdoctoral students from other departments.

6. Clinical Services N/A

7. Awards and Honors

Dr. Barr was elected president of the International Society for Developmental Psychobiology 2008-2009

Dr. Schechter was awarded the Pierre Janet Writing Award, International Society for the Study of Trauma and Dissociation, 2007

Dr. Fifer was selected as a member of the NICHD “Workshop on Antenatal Assessment”.

Dr. Gingrich was an invited speaker for the NIMH-Sponsored Julius Axelrod Symposium at the 2007 Society for Neuroscience Meeting

Dr. Gingrich was elected as a Full Member of the American College of Neuropsychopharmacology.

Dr. Gingrich was selected to be among the newly selected Simons Foundation Autism Research Scientific Group

Dr. Gingrich was selected to be the Chief Director of the Columbia University Frontier Fund.

New Grants

Hofer. Gift from the Sackler Foundation to fund a research program of interdisciplinary studies addressing the developmental role of the serotonin transporter in affective illness and its treatment.

Fifer. NIH U01, Co-Investigator on National Children's Study Vanguard Center (U01)

Williams and **Fifer.** Pilot Award, Irving Institute for Clinical and Translational Research (ICTR)

Sahni, **Fifer** and **Myers.** NICHD R21 to assess the effects of thermal stress and sleep position on autonomic reactivity during sleep in a group at increased risk for Sudden Infant Death, low birth weight newborns.

Myers and **Fifer.** Gift from the CJ Foundation to establish a fetal and infant physiology and behavior assessment at Columbia Medical Center.

Gingrich. NIMH R01 to examine environmental factors that contribute to the worsening or amelioration of the depressive phenotype found in the 5HTT knockout mice.

Gingrich. Gatsby Initiative pilot project to investigate the effects of global disruption of 5-HT_{2A} receptor (5HT_{2AR}) signaling in mice on conflict in anxiety.

8. Publications

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