Division of Developmental Neuroscience

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Overview

Research in the Division of Developmental Neuroscience focuses on understanding processes involved in the development of behavior and fundamental relationships between behavior and biology.

There are twelve investigators in the department studying 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 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.

Staff

Mark Ansorge, PhD, Research Associate
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, Sackler Institute for Developmental Psychobiology at Columbia
Christoph Kellendonk, PhD, Assistant Professor, Pharmacology & Psychiatry (Primary Department at NYSPI, Molecular Therapeutics)
Michael Myers, PhD, Chief, Research Scientist VI

Catherine Monk, PhD, Assistant Professor of Clinical Psychology (Primary Department at NYSPI, Biobehavioral Medicine)
Daniel Schechter, MD, Research Associate
Harry Shair, PhD, Research Scientist VI
Martha Welch, MD, Assistant Clinical Professor
Christoph Wiedenmayer, PhD, Research Associate

Current Research

Research in this department covers a very wide range of topics related to brain and behavior development and vulnerability to disease. One goal is to determine as early as possible whether individuals are at risk for subsequent neurobehavioral disorders. For example, in Dr. Michael Myers' work, 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. Catherine Monk, William Fifer, and Michael 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.

Within the Sackler Institute, Drs. Myron Hofer, Susan Brunelli, William Fifer, Jay Gingrich, Mark Ansorge, and Michael Myers were in the first year of new funding from the Sackler Foundation for a set of inter-connected research projects, under the overall direction of Dr. Hofer, on the developmental roles of serotonin receptor function. This research focuses on 3 major projects:

- the effects of treating 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.

In an animal model of infant affilative bonds, Drs. Harry Shair, Michael Myers, Holly Moore (Lieber Center), and Jeff Muller (Developmental Neuroscience) showed that endogenous dopamine secretion regulated a comfort response to the mother, but did not influence the response to littermates. These results are consistent with the literature linking the neural mechanisms of affiliation and reinforcement. This is also the first demonstration that the neurochemical substrates of an infant comfort response to dams differ from a behaviorally similar response to siblings.

Dr. Christoph Wiedenmayer's current research continues to focus on the development of defensive behavior and fear in early life. In young rats, he studies the role of the prefrontal cortex in emotion regulation, the neural bases of fear learning, and the effects

of early experience on fear responsivity later in life. Knowledge of the changes in the neural substrate underlying fear is central for our understanding of the developmental plasticity of emotional states.

Dr. Susan Brunelli has expanded her work on a genetic model of infant separation anxiety to include studies in collaboration with Dr. Frances Champagne and Dr. James Curley in Psychology at Columbia's downtown campus. They recently showed that rat mothers selectively bred to express low levels of anxiety as infants, engage in more active mothering. These results parallel findings that offspring of mothers showing more active maternal behavior are more resistant to stress at many levels than offspring of mothers showing less active maternal behavior.

Following a high profile report in Science by Drs. Mark Ansorge and Jay Gingrich, which showed that brief early postnatal exposure to FLX leads to behavioral changes in adult mice consistent with an increase in anxiety/depression-like characteristics, these investigators recently completed a study which amplifies these original findings. The new study not only replicates the apparent paradoxical effects of serotonin reuptake inhibition during early development but shows that these effects are specific to manipulation of the serotonin system; inhibition of norepinephrine reuptake during early development had no such long-term consequences on anxiety and depression profiles.

Under the leadership of Drs. Martha Welch and Michael D. Gershon (Pathology), the Columbia Brain-Gut Initiative continues to employ a multi-disciplinary research approach to better understand the effect of biological mechanisms of nurture on the body's immune, endocrine, autonomic, and behavioral regulation. Most recently, Dr. Welch has initiated a new study, currently in a pilot phase, which focuses on the effects of nurture intervention to optimize development of pre-term births in the Neonatal Intensive Care Unit. The study is a collaboration between Columbia University Medical Center Departments of Psychiatry and Pediatrics, and involves Drs. Michael Myers and William Fifer as Co-Investigators. Dr. Beatrice Beebe (Child Psychiatry) will measure maternal-infant behavioral changes in the enrolled infants during the early postnatal period.

Education and Training

The Division 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 25 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. During this year, the Division submitted a competing application for continuation of this grant. In June we were notified that this application was successful and that the program would be funded for an additional 5 five years. The department also sponsors the training and research of several undergraduate and graduate students, as well as postdoctoral students from other departments. In addition, Drs. Fifer and Myers were appointed to the advisory board of a RIMI (Research Infrastructure in Minority Institutions) grant at Mercy College. These

programs are designed to promote the education, training and development of young faculty at institutions with primarily minority students.

Grant Awards

National Institutes of Health and National Institute of Mental Health

Dr. Mark Ansorge, PI
Developmental Origins of Affective Disorders
This grant will investigate how developmental perturbations in serotonin signaling affect raphe function as it relates to anxiety- and depression related behaviors. The results will increase our understanding of (1) how certain genetic variants create vulnerability to neuropsychiatric disorders; and (2) the consequences and safety associated with fetal SSRI exposure during pregnancy. (NIH Pathway to Independence (PI) Award **K99 MH083044-01A1)**

National Institute of Mental Health

Dr. Raymond Booth, Dr. Jay Gingrich, Co-PIs
Serotonin 5HT2C Agonist Drugs with 5HT2A/B Antagonist Activity
This project proposes preclinical evaluation of (-)-trans-PAT as pharmacotherapy for obesity and neuropsychiatric disorders, and synthesis of PATs with enhanced 5HT2C agonist activity; PATs with potent 5HT2A/5HT2B antagonism may lead to drugs for psychiatric and cardiovascular diseases. **(1R01 MH081193-01A1)**

Dr. Jay Gingrich
Serotonin and the Modulation of Brain Development
This is a five year project that will increase our understanding of which developmental periods are sensitive to the unexpected effects of serotonin reuptake inhibition and the mechanisms that might explain these phenomena. **(1 R01 MH080116-01)**

National Institute of Drug Abuse

Dr. Jay Gingrich, Co-PI of Project 3
Hallucinogens on 5-HT2A Receptors: Mechanisms and Effects
This is a five year project to examine the role of 5-HT2A receptors in the mechanism of hallucinogens such as LSD. The studies propose to generate several knock-in mutations of 5-HT2A receptors that selectively perturbs
different aspects of receptor function (ligand binding, G-protein coupling, desensitization). **(P01 DA12923)**

Private Grants

Dr. Daniel Schechter (The Gertrude von Meissner Foundation in Geneva, Switzerland)

This award provides two years of support for MRI studies of neural activation of mothers with PTSD versus without, in response to viewing their own and others' children in different states of mind.

Dr. Jay Gingrich (Simons Foundation Autism Research Initiative)
Identification of Aberrantly Methylated Genes in Autism: The Role of Advanced Paternal Age
This project will identify specific loci that are most prone to aberrant methylation with advancing age, and are transmitted frequently to affected offspring.

Dr. Susan Brunelli (Award from the Columbia Brain-Gut Initiative)
Relationship between maternal nurturing behavior, oxytocin levels and gut lesions in High and Low USV rats.
This one year pilot study investigates epigenetic effects of maternal behavior in lines of rats selectively bred to express either High and Low levels of ultrasonic vocalizations during isolation in infancy.

Awards and Honors

Dr. Myron A. Hofer gave the 50th Sandor Rado Lecture, “The Emerging Synthesis of Development and Evolution: A new Biology for Psychoanalysis,” on June 3, 2008 at the NY Academy of Medicine. The Association for Psychoanalytic Medicine and the Alumni of the Columbia Psychoanalytic Center presents this award annually.

Highlights

Dr. Myron A. Hofer gave the 50th Sandor Rado Lecture on June 3, 2008 at the NY Academy of Medicine.

Dr. Schechter received the Pierre Janet Award for Best Scientific Paper from the International Society for Trauma and Dissociation

Two new RO1s (Dr. Jay Gingrich), 1 K-Award (Dr. Mark Ansorge), 3 awards from private foundations (Drs. Jay Gingrich, Susan Brunelli, Daniel Schechter).

New Faculty

Christoph Kellendonk, PhD
Joint appointment in Pharmacology and Psychiatry, within NYSPI,
Joint appointment in Pharmacology and Therapeutics and Developmental Neuroscience.

Mark Ansorge, PhD
Newly appointed as Research Associate.

Publications

Ansorge MS, Morelli E, Gingrich JA. Inhibition of serotonin but not norepinephrine transport during development produces delayed, persistent perturbations of emotional behaviors in mice. J Neurosci. 2008;Jan 2;28(1):199-207.

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