# Table of Contents

<table>
<thead>
<tr>
<th>Part I</th>
<th>Introduction</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Highlights</td>
<td>1-3</td>
</tr>
<tr>
<td>Part II</td>
<td>Research Programs</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1. Basic Science Division</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2. Behavioral Neuroscience Division</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>3. Clinical Research Division</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>4. Developmental Neuroimaging Laboratories</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>5. Sackler Awardee</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Addendum</td>
<td>31</td>
</tr>
<tr>
<td>Part III</td>
<td>Financial Report</td>
<td>enclosure</td>
</tr>
</tbody>
</table>
This report covers the fifth year of operation of the Sackler Institute, established at Columbia April 27th 2001 with a gift from the Sackler Foundation made in December 2000. The Institute is an organization within the College of Physicians and Surgeons and the Department of Psychiatry that brings together federally funded scientists active in research on the developmental origins of vulnerability to psychiatric illness. Our faculty brought in more than 10 million dollars in outside support last year. The income from the endowment supports a professorship for the Director of the Institute, and made a major contribution to the construction of the new Sackler Laboratories at the New York State Psychiatric Institute. In addition, it provides support for new directions in faculty research and funds the annual Sackler Award, a stipend for a postdoctoral fellow/junior faculty worker to facilitate their transition to becoming an independent researcher. In the past year the Institute sponsored conferences and symposia at national and international meetings, made 'mini-grants' to selected Sackler Fellows for their research costs, gave 'small seed money' grants for novel research pilot studies that enable subsequent grant applications for federal support, and provided administrative support for the Institute. An additional gift is supporting a special project on the early developmental role of serotonin transporter function.

The administrative structure and faculty of the institute over the past year were as follows:

Director, Dr. Myron A. Hofer  
Assistant Director, Dr. William P. Fifer  
Administrator, Jennifer Knowles  
Chief, Basic Science Division - Dr. Thomas Jessell  
Chiefs, Behavioral Neuroscience Division - Drs. Michael Myers and William Fifer  
Chief, Clinical Division - Dr. Myrna Weissman  
Head, Developmental Neuroimaging Laboratory - Dr. Bradley Peterson  
Head, Mouse Genetics and Behavior Laboratory – Dr. Jay Gingrich  
Liason, Cornell - Sackler Institute - Dr. Jonathan Polan  
Sackler Awardees: Dr. Mark Ansorge and Dr. Jonathan Polan

The research programs of the faculty and the two current Sackler Awardees are described in the second section of this report along with their publications for the year and their current Federal and other grant support. A financial report is available separately.

Part I - Highlights

There were 7 excellent applications for the Sackler Award this year and we were able to fund three (one at $50,000 and two at 25,000/yr each). Dr. Amir Levine, a research associate in the center for Neurobiology and Behavior was awarded the full stipend for his project on molecular mechanisms that contribute to the epidemiological finding that the earlier in life the exposure to drug abuse takes place, the greater the likelihood of becoming addicted. Dr. Levine proposed that “Since addiction, like memory storage,
requires the synthesis of new proteins, this difference between adult and young brains is likely to be regulated at the level of gene expression through chromatin modulation.” Based on preliminary findings he proposes to investigate transcription activators such as CREB and fosB.

Dr. Rachel Marsh, a postdoctoral fellow in the NIMH funded Developmental Psychobiology training program, with which the Sackler Institute is closely affiliated, was awarded an NIMH K01 Mentored Research Scientist Development Award shortly after her selection for a Sackler Award by our committee. She was then funded at half the full level, to support a research technician for her studies. She will be working with Bradley Peterson in her project on the possible functional impairment of the frantostriatal brain circuitry of patients with Bulimia Nervosa that underlie abnormalities in habit learning, self-regulatory and impulse control recently described in some patients.

The third award, also at the half-stipend level, was given to Dr. Philip Grieve, assistant professor of Biomedical Engineering in the Department of Pediatrics, for his project to use his novel measure of spatial and temporal EEG integration, during sensory processing in young children (0-3) at risk for autism (younger siblings), in age matched, low-risk controls and in autistic children 3-6 years of age. This novel method of computerized EEG analysis, devised by Dr. Grieve, assesses the ‘coherence’ of brain activity (timing, integration and gating) that is highly likely to be sensitive to the known brain abnormalities of autism (local over-connectivity and long distance under-connectivity) and their associated information processing deficits. The long term aim of this work is to enable early diagnosis and treatment and thus lead to better long term outcome. Funding for these 3 projects begins July 1, 2006

With a Sackler Foundation gift, the special project on the Early Developmental Role of Serotonin Transporter Function was begun in the spring of 05. Five interlocking research projects are aimed at understanding the unique roles of serotonin in the developing brain that underlie two recent clinical findings: the paradoxical increased vulnerability to depression when serotonin transporter gene function is reduced in individuals with certain gene variants, the adverse clinical responses of children and adolescents to selective serotonin receptor inhibitor (SSRI) drugs, as well as newborns exposed in utero by SSRI treatment of maternal depression.

(1) Experimental studies in mice by Drs. Gingrich and Ansorge have found a paradoxical increase in vulnerability to depression-like behaviors following both targeted serotonin transporter gene deletion and treatment of infant /juvenile mice from 3-21 days postnatal with SSRI drugs. Their most recent findings have implicated changes in serotonin neuron function in locus coeruleus, somatosensory cortex and corpus collosum in adult brains of these mice. These studies have led to the recent award of a project grant from the NIMH. (2) Study of the genetic mechanisms will be undertaken at the clinical level by genotyping subjects in Dr. Weissman’s three generation study of depressed women, looking especially for serotonin transporter gene variants, and by the brain imaging component of this study under Dr. Peterson. Collection of blood DNA began May 2005 and 145 samples have been collected thus far. Our collection first concentrates on subjects who have undergone MRI. (3) Drs. Fifer and Monk are collecting data on fetal behavior and autonomic function in utero, in newborns and in
early infancy following maternal treatment with SSRI’s during pregnancy. (4) Dr. Raymond Stark and Marianne Garland in the department of Neonatology, have found in their pregnant baboon model, that both placental transport and fetal metabolism reduce fetal SSRI levels to well below those in the mother, while PET studies show intense levels of binding to placental serotonin transporter. This preliminary data enabled Dr. Stark to obtain an NIH “innovation” (R-21) grant to extend these studies over the next 3 years. (5) Drs. Myers and Brunelli, working in a rodent model, found increases in pain threshold, isolation distress and body weight, but no effects in motor or reflex systems in rat pups following maternal SSRI treatment. After acute treatment with SSRI’s in juvenile/adolescent rat pups, significant increases in impulsive behavior were observed. An NIMH grant proposal based on these findings is currently under review. (More detailed information can be found in the sections for individual faculty members and in the addendum provided by Dr. Stark on page 31).

This spring we had a number of guest speakers and visiting scientists who gave talks and seminars at the institute. On January 12, 2006, visiting scientist Dario Maestripieri gave a research seminar entitled “Maternal Attachment in Human and nonhuman Primates” and on March 23, 2006 Susan Anderson visited the department and gave a talk entitled “Brain Development, Stress and Antidepressants”. On May 4, 2006, Thomas O’Conner visited our department and gave us a presentation entitled “Early Experience and Human Development: Theory, Evidence and Implications” followed by Carol Shively on May 11, 2006 with her presentation on “Socially-Induced Depression in Adult Female Cynomolgus Monkeys”. On June 15, 2006 Bryan Kolb spoke at our fellows seminar on “Pre and Postnatal Factors in Brain Development and Plasticity”.

At the 2005 annual meeting of the International Society for Developmental Psychobiology, the Sackler Institute funded a symposium titled “Developing a Framework for Development” in which Dr. Hofer and two other scientists discussed their approaches to building a new general theory of development. Sackler funding also supported travel for students from Canada, Europe, New Zealand and Australia to attend this meeting.

Sponsored Symposia: At the 21st annual meeting of the Winter Conference in Developmental Psychobiology, we co-sponsored, with the Cornell Sackler, two symposia: “Attention, Memory and Emotion” and “fMRI Studies of Language Development”.

A ‘Mini-Grant’ of $6,000 was awarded to Dana Byrd, a post-doctoral fellows in our NIMH-funded training program for her current study entitled “Infant Neuro-Developmental Markers of Cerebellar-Mediated Psychiatric Disorders”

Part II - RESEARCH PROGRAMS

1. **Basic Science Division**

Dr. Thomas Jessell, Chief – Dissecting Interneuron Circuits That Coordinate Locomotion
Local interneuron circuits have a major role in the coordination of motor behaviors. The simple repetitive movements that underlie locomotion are generated by localized neural networks known as central pattern generators (CPGs). These circuits provide a modelsystem for studying how neuronal networks generate simple behaviors. The local interneuron circuits that contribute to the vertebrate locomotor CPG reside in the spinal cord and generate the elemental patterns of motor activity that underlie swimming and walking movements. Little is known, however, about the organization of the locomotor CPG circuit in walking mammals, in part because of the difficulty in identifying and manipulating its intrinsic interneuronal components.

One potential strategy for selective manipulation of defined sets of CPG interneurons has emerged from our studies on interneuron subtypes and their progenitors in the developing spinal cord. Like motor neurons, spinal interneurons can be distinguished by the restricted expression of homeodomain transcription factors. We have found that graded sonic hedgehog signaling specifies four cardinal sets of ventral interneurons-V0, V1, V2, and V3 neurons-each with a different intraspinal projection pattern and target connectivity. Genetic and physiological studies performed with the lab of Martyn Goulding (Salk Institute for Biological Studies) have shown that V0 interneurons have a key role in establishing left-right alternation in motor activity, and thus are critical elements of the interneuronal circuitry that directs locomotor behavior.

Yet the classical physiological descriptions of spinal interneurons indicate a greater diversity than is revealed by these four cardinal interneuron subsets. In recent studies, we have found that these major interneuron classes can be further subdivided, on the basis of transcription factor expression, into more discrete neuronal classes. The selectivity of transcription factor expression by subsets of interneurons thus provides a powerful and systematic way of assessing local interneuronal function, through the neuronal subtype-restricted expression of toxins that kill neurons or ion channel proteins that regulate their activity. In this way, it should be possible to dissect the core logic of the interneuronal circuits that gate sensory-motor transmission and generate the rhythm and pattern of motor output. More generally, our findings point to the utility of transcription factors as genetic entry points for the functional analysis of brain circuits and mammalian behavior.

**Publications: 2005-2006**


Grant Support

Howard Hughes Medical Institute 09/01/2005-08/31/2006 43%
Role: PI $613,992 (operating expenses)

Molecular Analysis of Vertebrate Neural Development
Research support from HHMI is focused on the inductive interactions that control neural identity in the spinal cord.
Overlap: There is no direct overlap between HHMI funding and the experiments outlined in this proposal.

RO1 NS33245 09/01/2005 – 08/31/2009 10%
Role: PI
Control of Motor Neuron Differentiation
The aim of this project is to study the mechanisms by which the diversity of different motor neuron subpopulation are generated.
Overlap: There is no overlap between this grant and the current application.

WELLT066790-C-02-Z
The Wellcome Trust 05/01/2002 04/30/2007 10%
Role: PI $293,732

Functional Genomics of the Motor Neuron
The aim of this projects is to define the molecular cascades and gene networks involved in the determination of two defined neuronal cell types.
Overlap: There is no overlap between this grant and the current application.
Regulated Gene Expression in Motor Neurons and Neuron Progenitor Cells
The aim of this proposal is to apply contemporary methods of gene manipulation in the mouse to the study of the origins of ALS and to the design of novel strategies to prevent the death of motor neurons that occurs in ALS and other neurodegenerative disorder.
Overlap: There is no overlap between this grant and the current application.

Analysis of ES Cell Derived Motor Neurons.
The aim of these studies are designed to optimize the procedures for introduction of ES cell derived spinal cord neurons into adult spinal cord in normal and injured states.
Overlap: There is no overlap between this grant and the current application.

The G. Harold and Leila Y. Mathers Charitable Foundation (E. Kandel, M.D.)
Molecular Approaches to cognition: The Development and Modification of Internal Representations within the Brain.
The aim of this project is to determine how individual genes contribute to the cellular properties essential for the development and maintenance of cognitive maps.
Overlap: There is no overlap between this grant and the current application.

The Functional and Signaling Pathways of the Chemokine Receptor CXCR4 in the Immune and the Central Nervous Systems.
The Primary goal of this proposed project is to elucidate the physiological function of CXCR4 in the immune and nervous systems.
Overlap: There is no overlap between this grant and the current application.

Motor Neuron Subtype Diversification: ES Cell Potentiability Deduced From Developmental Mechanism.
The overall goal of this proposal is to define the normal developmental mechanisms that promote the diversification of motor neurons into specific functional subtypes.
Overlap: There is no overlap between this grant and the current application.
2. **Behavioral Neuroscience Division**

Dr. William Fifer, Assistant Director - Human Fetal Behavior and Intrauterine Influences on Vulnerability to Psychiatric Illness

Our general research program focuses on the effects of the early environment on fetal and infant brain/behavior development. We are funded by NIH to investigate the effects of prenatal risk factors including maternal nicotine and alcohol use during pregnancy, as well as maternal stress and anxiety, on autonomic nervous system development. With Dr. Monk, from the Department of Behavioral Medicine, we continue our studies on the influence of maternal depression and anxiety on fetal and infant development.

With Dr. Myers we received an NIH MERIT Award to continue to study early markers of risk for Developmental Disorders and Sudden Infant Death (SIDS) in high-risk populations in Washington Heights and on the Pine Ridge Reservation in South Dakota. A further extension of this work, with the Department of Pediatrics, focuses on the developing nervous system in prematurely born infants and, together with colleagues from the Division of Environmental Health Science at Columbia, assessments of sleep dependent physiology in infants exposed to environmental toxins during pregnancy. During this past fiscal year we continue to receive NIH funding for two relatively new projects. One is to investigate sleep arousal mechanisms in at-risk infants from a database collected as part of the NICHD CHIME (Cooperative Home Infant Monitoring Evaluation network). We also received funding for five years for Phase II of an NIAAA/NICHD network to study the effects of alcohol on SIDS, unexplained fetal demise and other neurobehavioral disorders. This network focuses on high risk populations in South Africa and the Dakotas.

**SSRI project:** Drs. Monk and Fifer are continuing the clinical research arm of the SSRI project. They are investigating the effects of SSRIs during pregnancy on fetal and infant neurobehavioral development

**New Appointment for Dr. Fifer:**
Professor Extraordinary: Department of Obstetrics and Gynecology at Stellenbosch University, Capetown, South Africa.

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Dr. Myron Hofer, Director - Process of Attachment and the Regulation of Development

Our research has centered on the role of the parent-infant relationship as the first major environmental influence on postnatal development. I and my colleagues have explored how early maternal separation and different patterns of mothering exert long-term effects on vulnerability to disease. Through an experimental analysis of the psychobiological events that enmesh the infant rat and its mother, we are studying the hidden regulatory processes that are the basis for the early origins of attachment, the dynamics of the separation response and the long term shaping of development by that first relationship. My recent work has focused on a synthesis of recent research on the
psychobiology of early attachment, its role in later development and how these traits and their biological mechanisms have evolved from their animal origins.

I am currently working on a book on developmental processes, viewed from an evolutionary perspective. This has led me to attempt to answer, in a new way, questions such as: what is development? How is it related to evolution? And when and how did development evolve? My (not so modest) goal is to find relatively simple principles that can help us organize and think about the many different developmental processes that are being discovered nearly every day at levels from cells to society.

A special issue of the journal, Developmental Psychobiology, was published in recognition of the advances made by Dr. Hofer and his group over the past three decades.

Dr. Michael Myers, Division Chief - Early Nutritional Influences on Vulnerability to Disease

Work in this laboratory continues to investigate the relationships between inadequate nutrition during pregnancy, undergrowth of the fetus, and disease later in life. Many epidemiological studies have shown that vulnerability to cardiovascular disease, diabetes, schizophrenia, and depression are all influenced by nutritional disturbances during this critical period of development. Characterizing the long-term effects of early experiences remains of great interest to researchers in the field of Developmental Psychobiology. However, recent advances in molecular epigenetics make it now possible to study the proximal mechanisms and the developmental processes that account for enduring changes in disease vulnerability. This is a major focus of work in our group. In collaboration with Drs. William Fifer and Harry Shair in our department, and Dr. Morris Cohen at Newark Beth Israel Hospital, we investigate these phenomena in both animal models and human infants.

Our studies focus on effects of variation in nutrient availability in the perinatal period on physiological, biochemical and behavioral characteristics of newborn infants. Sensitive markers, ascertained from animal studies, are folded in to our human studies, and the underpinnings of correlative findings from human studies are pursued in animal models. These studies will determine if human infants with low birth weights, or rats whose mothers were underfed during pregnancy, express differences in cardiovascular and behavioral responses to feeding and postural challenge. We are also investing much effort in the discovery of early markers that will allow better detection of which infants may be at greatest risk for long-term vulnerabilities. In particular, we have expanded our studies of placental gene expression to include effects of caloric deficits, energy surfeits, as well as effects of drug exposure (SSRIs) and drugs of abuse (alcohol). Ongoing studies strongly support the hypothesis that profiles of placental gene expression will provide sensitive and specific markers for a wide variety of adverse prenatal events and exposures.
In addition to these studies, during the past year our division conducted studies in collaboration with Dr. Susan Brunelli that continue to examine effects of SSRI treatments during gestation on infant neurobehavioral outcomes, and acute effects of SSRIs on impulse control later in life. These animal model studies are supported by the Sackler Serotonin gift project. Two prenatal exposure studies were completed this year which support findings from clinical studies suggesting that one important effect of prenatal exposure to SSRIs is to alter (increase) pain thresholds during the early postnatal period. We also conducted a study which indicates that acute, but not chronic, treatment of juvenile rats increases impulsive behavior. These findings are important as they suggest a possible link between vulnerability to suicide and acute treatment with SSRIs.

Dr. Jonathan Polan, Liaison – Cornell-Sackler Institute

I am currently working in the laboratory of Dr. Eric Kandel at Columbia University's Center for Neurobiology and Behavior fusing developmental psychobiologic and genetic techniques to investigate new models of psychopathology. I am privileged to have been funded for this work by a Sackler Research Award from July 2004 through June 2006. (see Awardee Report p.28 for details)

Jay Gingrich, Head – Laboratory of Translational Neurogenetics

The Gingrich Laboratory is currently pursuing different lines of research related to the genetics of neuropsychiatric disorders. Mice offer an excellent model to understand the developmental contribution of genes to normal brain maturation and thus are employed extensively in our studies. Mice with transiently-reduced transporter function during early life matured into adult mice with numerous abnormalities in depression and anxiety-related behaviors. We are taking a multilevel approach to understand the underlying biology—using techniques of anatomy, electrophysiology, gene expression, and behavioral analyses. We also received an RO1 grant from NIMH to examine the biological underpinnings of environmental influences on mice with genetically-reduced SERT function. This work has also been supported by the Sackler serotonin initiative funded this year, in addition to the support received by Mark Ansorge, a current Sackler Awardee.

We have two projects directly related to schizophrenia, that have received NIMH funding support in the last year. Neuregulin1 (NRG1) has been identified as a susceptibility gene in schizophrenia. Mice with reduced expression of different NRG1 isoforms exhibit several behavioral abnormalities that are consistent with both positive and negative symptoms of schizophrenia. We have identified that these mice exhibit social deficits, olfactory deficits (as do some schizophrenics). We have found that these mice have underlying deficiencies in the targeting of newly generated neurons to the olfactory bulb. Thus, we are working to discover to what degree NRG1 is involved in brain development and to what degree it serves a maintenance function.
The second project examines the role of aberrant DNA methylation as a possible epigenetic contribution to schizophrenia susceptibility. Researchers at Columbia, working with Dolores Malaspina, have demonstrated that paternal age in excess of 45-50 years at the time of conception is a significant risk factor for the conceived offspring. We have developed an animal model of this phenomenon and are exploring the hypothesis that methylation accuracy of spermatagonia DNA decreases with increased number of divisions (as would occur over time in older fathers).

The fourth project examines the role of a major post synaptic receptor for the neurotransmitter serotonin 5HT2A in behavioral control of anxiety-like behaviors and in psychosis-related endophenotypes. We have recently developed the technology to specifically manipulate receptor signaling in specific brain areas. This will allow us to define the minimal circuits that are sufficient to mediate serotonin effects on anxiety and schizophrenia-related behaviors. This work was recently published in the journal, Science.

Dr. Gingrich was the recipient of the 2006 Roche-Nature Medicine Prize in Translational Medicine. He received this award at the end of a 2-day symposium where he presented the work of his laboratory.

Publications


Grant Support (dollar figures are per year)

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Last updated: 4/4/07
Subcontract with Dartmouth University to characterize and quantify spontaneous arousals during sleep from data previously recorded as part of a large home monitoring grant (CHIME).

U01 HD45935  10/01/03-9/30/06  8%
NICHHD $125,000 (total)  $21,198
(Myers and Fifer Co-investigators)

"Northern Plains Prenatal and Infant Health Consortium"
Phase I grant to design multi-site investigations of the effect of alcohol on stillbirth and sudden infant death syndrome in several reservations in the Northern Plains and in South Africa.

R01 ES08977 (Fifer Co-investigator)  04/01/02-03/31/07  5%
NIEHS $788,059
"Environmental Health in a Cohort of Minority Women/Infants"
To investigate the impact of pre- and post-natal exposures to air pollutants on fetal growth and early childhood neurobehavioral development.

R13 MH HD58769 (Fifer, W.P., PI)  10/01/00-9/30/10  1%
NIMH $15,000
"International Society for Developmental Psychobiology Student Travel Grant"

R01 HD32774 (Fifer, W.P., PI)  04/01/06 - 03/30/11  38%
NICHHD $363,300
"Perinatal Assessment of At-Risk Populations"
This is an investigation of underlying mechanisms and early assessment of risk for Sudden Infant Death.

U01 (Fifer and Myers, Co-PIs)  09/01/06 - 07/31/11
NICHHD $404,362  20%
"Prenatal Alcohol in Sudden Infant Death Syndrome and Stillbirth (PASS) Network"
Co-operative Agreement for Physiological Assessment Center

R01 ES11596 (Myers, M.M)  08/01/01-06/30/08  25%
NIEHS $312,612
"Fetal Origins of Disease: Markers, Modulators, Mechanisms"
These are animal model and human infant studies that focus on changes in cardiovascular function, glucose regulation, and gene expression associated with variations in early life growth and nutrition.

T32 MH018264 (Myers, M.M. and Hofer, M.A.)  07/01/03-06/30/08  5%
NIMH $250,066
"Research Training in the Psychobiological Sciences"
Postdoctoral research training grant for MDs and PhDs in Psychobiology.
U01 HD45935 (Elliot, A.)  10/01/03-09/30/06  5%
NICHID       $125,000
(Myers, M.M., Co-investigator)
"Northern Plains Perinatal and Infant Health Consortium"
This is planning grant to design multi-site investigations of the effects of maternal
alcohol consumption on stillbirths and sudden infant death syndrome.

R01 HD32774 (Darnal, R.)  04/01/06-03/31/11  5%
NICHID       $379,054
(Myers, M.M., Co-investigator)
"Spontaneous arousals in “CHIME” Infants at Risk for SIDS"
This grant will characterized and quantify spontaneous arousals during sleep from data
previously recorded as part of a large home monitoring grant (CHIME).

R01 HD32774 (Fifer, W.P.)  04/01/06 - 03/30/11  15%
NICHID       $363,300
(Myers, M.M., Co-investigator)
"Perinatal Assessment of At-Risk Populations"
This is an investigation of underlying mechanisms and early assessment of risk for
Sudden Infant Death.

P20 MD001631(Perryman, B.)  09/30/05-06/30/10  10%
NCMHHD       $90,886
(Myers, M.M., Co-investigator)
(subcontract)
"Center for Health Research with Tribes in SD-MT-WY." Project IV, “Early predictors of
Adverse Neurobehavioral Outcomes in Young Children”
To help institutions build the infrastructure to support community-based participatory
research on health disparities.

NIMH(RO1-MH076026-01) (Gingrich)  07/01/06 to 06/30/10
$250,000
Gene - Environment Interactions in 5-HTT Deficient Mice.
This study examines the environmental factors that contribute to the worsening or
amelioration of the depressive phenotype that have been described in the 5HTT
knockout mice.

NIMH (R21 MH073794-01) (Gingrich)  03/17/05 to 02/28/07.
$150,000
Epigenetic mechanisms: Paternal Age and Disease
2 year project to investigate the role of aberrant sperm methylation as a mechanism for the risk advanced paternal age poses for their offspring to several diseases, including schizophrenia.

Conte Center for the Neuroscience of Mental Disorders (P50MH066171-01A1) (Lieberman)(Gingrich) 07/01/04 to 06/30/09. $50,000

Our component of this Center uses mice partially deficient in neuregulin-1 as an animal model of schizophrenia. Role on Project: Co-PI Project 6

Conte Center for the Neuroscience of Mental Disorders The Neurobiology of Suicidal Behavior (2 P50 MH062185-06) (Mann)(Gingrich) 07/01/05 to 06/30/10. $50,000

Project 6- Genetic Modulation Of Serotonin During Development: Models Of Aggression, Impulsivity And Depression (PI: Underwood) Our component of this Center Animal Project (7) examines the development of behavior in SERT and MAOA KO mice to understand the divergent effects of each genotype on behavior. Role on Project: Co-PI.

Whitehall Foundation (Gingrich) 01/01/05 to 12/30/07 $75,000
Role of Cortical 5-HT2A receptor expression in hallucinogen function.
3 year project to identify the role of cortical 5-HT2A receptors in the mechanism of action of LSD-like hallucinogens.

American Foundation for Suicide Prevention (Gingrich) 02/01/05 to 01/31/06 $10,000
Role of Cortical 5-HT2A receptors in impulsivity and aggression.
To examine the role of serotonin 5-HT2A receptors as possible mediators of impulsivity and aggression with the goal of identifying medications that may reduce these characteristics in susceptible individuals.

NARSAD (Ansorge) 07/15/05 to 07/14/07 $30,000
Consequences of SERT Inhibition during Development on Adult Behavior and Neurophysiology. 2 year project to investigate the disruption of SERT function during critical developmental periods may alter the trajectory of the central nervous system development in ways that influences affective function later in life. Role on project: Postdoctoral Mentor

Gatsby Initiative in Brain Circuitry(Gingrich) 02/15/06 to 02/14/08 $50,000
Genetic Dissection of Complex Signaling Pathways in Schizophrenia.
A 2 year Gatsby Pilot Project to investigate the global disruption of 5-HT2A receptors (5HT2AR) signaling in mice reduces inhibition in conflict in anxiety paradigms without affecting fear-conditioned learning and depression related behaviors. These findings indicate a specific role of cortical 5HT2AR function in the modulation of conflict anxiety—an effect dissociated from depression and fear and consistent with models of cortical, “top-down” modulation of anxiety.

Role on Project: PI

Sackler Institute Fellowship Award (Ansorge) 07/01/04 to 06/30/07 $45,000

Early Life Inhibition of the Serotonin Transporter Alters Emotional Behaviors in Adult Mice.
Identification of a developmental mechanism to explain how various genetic polymorphisms that alter serotonergic signaling (e.g., serotonin transporter 5HTT-LPR or MAOA gene variants) may predispose individuals to increased vulnerability to emotional disorders later in life.
Role on Project: Post Doctoral Fellowship

NIMH(RO1-MH076026-01) (Gingrich) 07/01/06 to 06/30/10 $250,000

Gene - Environment Interactions in 5-HTT Deficient Mice.
This study examines the environmental factors that contribute to the worsening or amelioration of the depressive phenotype that have been described in the 5HTT knockout mice.
Role on project: Co-Investigator

3. **Clinical Research Division**

Dr. Myrna Weissman, Chief - Clinical Epidemiology Studies of Genetic Risk and Biological Markers in the Development of Mood and Anxiety Disorders

Our goal is to understand the risk for mood and anxiety disorders across generations. We have followed and clinically characterized samples of patients with mood and anxiety disorder or at high risk for these disorders. We are using genetic, neuropsychological, and neuroimaging studies to better understand the pathophysiology and neural circuitry of these disorders, and are adding a genetic component to imaging studies and vice versa.

A major focus includes a three-generation study of offspring at high and low risk for depression. The study has had four waves of assessments for over 20 years and a fifth wave underway. The 20 year follow up of the second generation found continuing recurrent depression in the high risk group and an increase in medical problems, particularly cardiovascular disease and increased mortality as they enter middle age (Weissman et al, 2006). We examined the association of 2 distinct types of anxiety disorders; fear-related and context-related anxiety disorders which were defined as panic or phobic disorders and generalized anxiety or overanxious disorders.
respectively. Fear-related anxiety disorders are thought to be associated with dysregulation of circuitry dependent on the amygdala and context-related with dysregulation of circuitry dependent on the hippocampus or bed nucleus of the stria terminalis. We determined that it was only fear – and not context-related anxiety disorders that partially and in adolescence completely explained the increase for depression in generations 2 and 3 of high-risk subjects. Extending the clinical findings we examined the association of variability in fear-potential startle response with anxiety and depressive disorders. Both the baseline and fear-potentiated startle response were associated with fear-related anxiety. Once the 5th wave of data collection is completed we will determine if variability in startle response predicts new onsets of anxiety or depressive disorders.

In collaboration with Dr. Bradley Peterson we are conducting functional and anatomical magnetic imaging studies in this and are developing hypothesis about brain endophenotypes using the EEG and startle data. We have thus far completed 187 structural and 179 functional MRIs. Studies in children and adults suggest the EEG measures of regional hemispheric asymmetry, i.e., the difference in activity over right and left brain regions, may be potential markers of vulnerability to depressive disorders. (Bruder et al., 2005), Grandchildren with the highest risk for a MDD displayed a posterior alpha asymmetry that resembles that seen for 2nd generation offspring of parents concordant for MDD and for adolescents or adults having a depressive disorder. This supports the hypotheses that this EEG asymmetry may be a biologic marker of vulnerability for the development of MDD (Bruder et al, submitted 2006).

We assessed the morphology of cortical surfaces and thickness of the cortical mantle in 115 of the 2nd and 3rd generation members of the 3-generation cohort of individuals who are at either high or low familial risk for depression. In 55 high risk compared with 60 low risk subjects, we detected a significant lateraled protrusion of the cortical surface in the inferior parietal and posterior temporal regions in the right hemisphere. These findings suggest that a relative hypertrophy of underlying white matter is responsible for protrusion of the cortex in these regions, despite a thinning of the neighboring and overlying cortical mantle. We are currently analyzing white matter in these images to confirm the presence of localized hypertrophy. A lifetime history of depressive or anxiety disorders did not account for these group differences, suggesting that the abnormalities may represent trait vulnerabilities for developing depressive illness.

We are using Sackler serotonin project gift funds to collect samples of DNA to study the influence of genetic polymorphism on morphology of cortical surface in the sample. Collection of blood DNA began May 2005 and we have collected 145 samples thus far. Our collection first concentrates on subjects who have undergone MRI.

We have followed up previous findings on the high familiality of recurrent major depression beginning before the age of 30. As participants in the multi-site study to identify major depression susceptibility gene, the collection of about 1000 sib pairs with recurrent early onset major depression has been completed. Biological material and clinical data is being shared with the scientific community and data analyses are underway (Holmans et al submitted, Levinson et al submitted). The renewal of this grant has been approved for 4 more years funded in 9/05 to follow up findings and

Last updated: 4/4/07
collect an additional sample. We are discussing adding an imaging component to this study and will use Sackler funds for pilot feasibility studies.

Work is ongoing to understand the genetic basis of fear and anxiety disorders in humans by identifying variants forms of genes that may contribute to pathological anxiety state in mice. Candidate genes that are identified from the study of learned and innate fear in mice are being tested in a sample of normal humans with various degrees of fear conditioning, following startle test, as well as patients with panic disorders, social anxiety disorders, and normal controls. The collection of the clinical sample and 75% of the normals are completed. We obtained access to an additional control sample from NIMH. The early results were presented at Cold Spring Harbor (Suresh et al 2006, Talati et al, 2006). The samples are being genotyped with dense simple nucleotide polymorphism (SNP) markers spanning major candidate genes. In collaboration with Joy Hirsch, PhD, we have begun pilot work to collect structural and functional MRI scans.


Grant Support (dollar figures are per year)

Myrna M. Weissman, Ph.D.

5 RO1 MH60912-05A2 (Weissman) 09/22/05 - 06/30/09
NIH/NIMH $323,320
Genetics of Early-Onset Major Depression
A six-site cooperative project to collect a large sample of subjects with early-onset MDD obtaining clinical data and genetic samples aiming to map genes giving a susceptibility to MDD. This is a renewal of a collaborative study.

2 RO1 MH28274-26 (Weissman) 07/08/03 to 06/30/06
NIH/NIMH $265,160
Genetic Studies of Depressive Disorders
This is a project to understand the etiology of panic disorder using a broad range of novel and advanced genetic and epidemiologic approaches.

5 R01 MH63852-05 (Weissman) 07/19/01 to 06/30/07
NIH/NIMH $526,225
Children of Depressed Mothers: a STAR*D Ancillary Study
The overall aim is to study the impact of a reduction of maternal depressive symptoms on children’s psychiatric symptoms and social functioning as an ancillary study to the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D).

2 T32 MH16434-21 (Shaffer) 07/01/05 to 06/30/10
NIH/NIMH $455,440
Research Training in Child Psychiatry
The Child Psychiatry Research Training Program trains postdoctoral psychiatrists, psychologists, and others to become independent investigators in the field of child and adolescent psychopathology. The grant supports ten M.D. and/or Ph.D. trainees for up to three years.

P30 MH071478 (Shaffer) 06/1/04 to 05/31/09
NIH/NIMH $1,274,194
(Weissman PI of Principal Research Core [PRC])
ACISR for Pediatric Psychiatry Disorders
The ACISR consists of four cores that work with another to: develop and transport effective treatment for pediatric psychiatric disorders in the community; identify problems in the methods used in intervention research with children and adolescents; and work with basic-scientists to investigate whether state of the art imaging and genotyping methods can be used to identify the mediators of treatment response.

5 R01 MH 36197-22 (Weissman) 01/01/03 -12/31/07
NIH/NIMH $608,101
Children at High and at Low Risk for Depression
Overall aim of this study is to understand the long-term temporal sequence and familial patterns of mood and other disorders from childhood to adulthood in offspring at high and low risk for depression. The study now includes three generations. The aims during this project period are (1) to complete data analyses of the 4th wave of assessments; (2) acquire and analyze both anatomical and functional MRI in 214 subjects; (3) conduct data analyses integrating clinical, psychophysiological, and neuroimaging studies.

5 R01 MH 36197-22 (Weissman) 01/05/06 -12/31/07  
NIDA Suppl to above $105,756

Children at High and at Low Risk for Depression  
The aims are (1) To examine the longitudinal course of drug use and smoking, including risk factors that lead to drug use and smoking, and the course of drug use and smoking from childhood to adulthood. (2) To examine the impact of parental drug use and smoking on functioning and psychopathology (including substance use) in offspring, as well as the impact of maternal drug use and smoking during pregnancy on child outcomes. (3) To search for differences in brain function and structure that may account for substance use and other psychopathologies, using (a) electroencephalography (EEG), (b) startle, (c) Magnetic Resonance Imaging (MRI), comparing individuals with and without drug use disorders, as well as individuals at high and low risk (by virtue of their family history) for drug use disorders.

1 P01 MH60970-04 (Weissman) 01/01/03-12/30/06
NIH/NIMH $172,279 (Project 4 only)
(PI of Project 4 “Clinical Studies of Human Anxiety) (Program Project Grant in collaboration with C. Gilliam, E. Kandel, R. Hen, and A. Fyer)

Molecular Genetic Studies of Fear and Anxiety  
To study the molecular and genetic basis of amygdala-regulated fear and anxiety in mice and humans. Several fear conditioning paradigms will be studied in both mice and humans, along with selected anxiety related traits and disorders in humans. Genes that alter fear-conditioning phenotypes in mice will be analyzed for trait-related DNA sequence variation in humans who score at the phenotypic extremes for the matched paradigm. Genes shown to alter other anxiety measurements in mice will be analyzed for trait or disorder-related variation in humans with a variety of anxiety-related temperaments and disorders.

1 P60 MD000206-03(Carrasquillo) 10/01/02-9/30/07
NIH/NCMHHD $78,413 (Core Only)
Columbia Center for the Health of Urban Minorities - Core 7 (Olfson)
The overall aim of the Mental Health Research Core is to facilitate the development and research evaluation of mental health interventions for low-income minority populations

Josiah P Macy Foundation (Weissman) 07/01/03-06/30/06 $200,000

Bridging the Gap Between Research and Clinical Practice in Modern Psychotherapy

Last updated: 4/4/07
The overall goal is to decrease the considerable gap that now exists between the availability of evidence based treatments (EBT), particularly psychotherapy, and training of clinical practitioners, in psychiatry, psychology, and social work, who actually provide psychotherapy to the patients.

NARSAD Distinguished Investigator Award  5/1/05-04/30/07  
(Weissman)  $100,000  
Three Generations at Risk for Depression: Genetic Studies  
To collect RNA for gene expression studies in collaboration with Steven P. Hamilton, M.D, Ph.D. and Victoria Haghighi, Ph.D.

4. Developmental Neuro-imaging Laboratories

Dr. Bradley Peterson, Chief – Normal Brain Development and the Neural Basis of Psychiatric Disorders

**Funded Projects**

Dr. Peterson received funding for a midlevel Career Development Award that will support a portion of his salary for research and mentoring activities.

Dr. Rachel Marsh, a fellow in our NIMH funded postdoctoral training grant, received a Career Development Award (K01), which will provide salary support and pilot funding for a period of 5 years. She received a Sackler Award to facilitate this research – see Part I Highlights.

Collaboration with Drs. Myrna Weissman of the Sackler Institute has continued in our funded R01, and we have thus far successfully scanned 190 individuals in a large, 3-generational cohort that has been followed by Dr. Weissman over the past 20 years. Individuals in all 3 generations who are at either high or low risk for major depressive illness are being studied with MRI and with neuropsychological tasks designed to test the integrity of neural systems thought to be dysfunctional in depression. Blood samples are being drawn for genotyping and correlation with both MRI and clinical data. Data analyses continue in preparation for the first report on the imaging data collected from this cohort.

On a funded R01, recruitment is proceeding rapidly for the imaging of newborn infants exposed prenatally to crack cocaine, narcotics, or marijuana. We are using MRI to assess brain structure, connectivity, and neurometabolites in these drug-exposed infants compared with unexposed controls. We have established a large network of recruitment sites in drug treatment centers and obstetric clinics throughout the greater New York metropolitan area.

On another funded R01, we are analyzing MRI data from 620 MRI scans obtained in children and adults who have Tourette syndrome, OCD, or ADHD, or who are healthy comparison subjects. Brain-based correlates of morphological measures with performance on cognitive tasks, with brain activity on fMRI scans, and genetic variation are being assessed.
Dr. Peterson is the PI on a grant received from the Simons Foundation to assist in the collection of DNA samples from a large sample of Autistic individuals and their parents. He has also begun obtaining MRI scans in those same individuals, with the aim of understanding how genetic variants influence brain structure, function, and connectivity in children with Autism.

Various faculty within the MRI unit have published a series of papers that have advanced the technology and methods for the analysis of anatomical and diffusion tensor images, which will aid in the understanding of brain structure and connective circuits within the CNS.

Publications


Grant Support

1 K02 MH074677-01 7/01/05-6/30/10
NIMH $113,760

MRI In Childhood Neuropsychiatric Disorders
This is a midlevel Career Development Award to use Magnetic Resonance Imaging (MRI) methodologies to identify the neurobiological basis of developmental neuropsychiatric disorders, particularly in: (1) Disorders of impulse control, including Tourette’s syndrome, Obsessive-Compulsive Disorder, and Attention-Deficit/Hyperactivity Disorder; 2) Conditions that confer risk for disturbances in development of the neonatal brain, including premature birth and prenatal exposure to drugs of abuse; and 3) Affective Disorders. A substantial portion of his work also involves the development of new methods for processing MRI data and for translational research involving behavioral neuroscience paradigms within the MRI scanner, as well as mentoring junior investigators in the application of neuroimaging methodologies to the study of childhood psychiatric disorders.

Role: PI

Last updated: 4/4/07
Children at High and Low Risk for Depression
This study aims to identify the brain-based correlates of children and adults at high or low risk for depressive illness using anatomical and functional MRI.
Role: Co-PI

DA017820 (B. Peterson, PI) 4/01/04-3/31/09
NIDA $424,948
MRI of Infants Exposed Prenatally to Drugs of Abuse
To define the effects of drugs of abuse on brain structure and metabolite concentrations, as well as the behavioral correlates of those effects, in infants and children who have been exposed to drugs of abuse during fetal development.
Role: PI

1 R01 MH070424-01- (C. Hoven, PI) 6/01/04-5/31/05
NIMH $426,563
WTC Impact, Familial Transmission and Child PTSD
To conduct a Pilot Study grew out of our findings from a large epidemiological study of New York City public school children (N=8,200) six months post-9/11, which identified higher than expected rates of probable psychiatric disorders in children, most especially among children of World Trade Center (WTC) evacuees.
Role: Director of the MRI research component of the project.

R01 MH068318 (B. Peterson, PI) 10/01/04-9/31/08
NIMH $450,000
Neuroanatomical MRI Studies of Childhood Disorders
To understand normal brain development and the neural basis of childhood neuropsychiatric disorders using anatomical MRI.
Role: PI

1 P30 MH071478-01 (D. Shaffer, PI) 06/01/04 - 05/31/09
NIMH $1,019,681
ACISR for Pediatric Psychiatry Disorders
The proposal outlines four cores that will work with another towards the following goals:
1) To promote and develop efficacy studies in disorders of interest to investigators of the Center where the evidence-based support for interventions remains substantially deficient and where “export” into the field would be premature. 2) To study transportability and effectiveness of interventions or methods of evaluation for which there is substantial evidence-based support, to real world settings. 3) To identify problems in the methods used in intervention research with children and adolescents.
4) To work with basic-scientists to investigate whether state of the art imaging and genotyping methods can be used to identify the mediators of treatment response. 5) To train new intervention researchers; and 6) To take a scientific and advocacy leadership role in promoting and disseminating intervention research.
Role: Co-investigator

Last updated: 4/4/07
Research Training in Child Psychiatry

The Child Psychiatry Research Training Program trains postdoctoral psychiatrists, psychologists, and others to become independent investigators in the field of child and adolescent psychopathology. The grant supports ten M.D. and/or Ph.D. trainees for up to three years.

Role: Co-Investigator

Lilly Research Laboratories
7/1/06-6/30/07
(D. Hellerstein & B. Peterson, Co-PIs) $150,125

Functional and Anatomical MRI changes after treatment of chronic depression with Duloxetine

The purpose of this study is to evaluate pre- and post-treatment anatomical and functional MRI findings for a subset of the outpatients enrolled in a double-blind study of duloxetine vs. placebo in outpatients with chronic depression.

Role: Principal Investigator

MRI Studies of the Effects of Environmental Toxins on CNS Development
(Z. Dong, P.I) 4/01/06 – 3/31/07
Center for Environmental Health in Northern Manhattan $25,000

The aim of this project is to use Magnetic Resonance Imaging (MRI) to define the effects of prenatal and early postnatal exposure to various environmental toxins on the structure, metabolism, and anatomical connectivity of the brain in 60 5-year old children.

Role: Co-PI

An fMRI Study of the Neural Basis of Transference in Healthy Young Adults
(A. Gerber, P.I) 06/01/06 – 05/31/07
International Psychoanalytic Association $10,000
American Psychoanalytic Association $17,000

The goal of this grant is to measure brain activation associated with transference and set the stage for future research that tests psychoanalytic hypotheses about the role of transference in psychopathology and psychoanalytic change.

Role: Co-PI

fMRI Study of Affect (D. Gorman, P.I) 01/01/06 – 12/31/06
AACAP $9000

The purpose of this study is to identify the neural systems that subserve emotion using functional magnetic resonance imaging (fMRI). Data already collected in adults will be analyzed, and then the methodology will be refined and applied to adolescents.

Role: Co-PI

A DTI Study of Anatomical Connectivity in Adolescents with Bipolar Disorder
(D. Xu, P.I) 7/1/05 – 6/30/07
NARSAD $30,000
The aim of the study is to identify abnormalities in anatomical connectivity of brain regions believed to be involved in the pathophysiology of adolescent-onset of Bipolar Disorder.

Role: Investigator

5. **Sackler Awardees**

Jonathan Polan

In the past year, I showed that a mouse generated in this lab to model schizophrenia by over-expressing the dopamine D2 receptor in the striatum, acquires its adult phenotype of working memory and social interaction deficits during pre- or early postnatal development. To model the “double hit” hypothesis of schizophrenia I am investigating the interaction of prenatal restraint stress with the genetic vulnerability. My hypothesis is that the transgenic animals that were prenatally stressed will demonstrate a synergism between the genetic vulnerability and the environmental manipulation by developing more severe schizophrenia-like symptoms than either stressed or transgenic animals alone. The data so far show an effect of prenatal stress, validating the method. Because a large number of litters is needed to show a statistical effect of the interaction of the stress and the transgene, I anticipate having evidence for or against the interaction hypothesis in the next several months.

At the same time, I generated another transgenic mouse model of dopamine-related psychopathology, which over-expresses the gene for catechol-O-methyl transferase (COMT), an enzyme responsible for the metabolism of dopamine at brain synapses. I already have more than 5 founder animals, which are being mated. These matings will produce adult offspring for molecular biological and behavioral phenotypic analysis. Like the excess D2 receptor animal, the COMT transgene is restricted to the forebrain and under temporal control by a molecular switch, which can be turned off at will.

These two transgenic animal models should provide complementary views of the developmental psychopathology involving forebrain dopamine systems. In conjunction with my work on these two animal models, I collaborated on a study of humans which showed that working memory is impaired by a combination of genetic polymorphisms that over-express the D2 receptor.

In a separate project, which directly extends my prior work in the Sackler Institute on early mother/infant attachment, I found genetic effects on maternally directed orienting behaviors (MDOBs), the neonatal behaviors that I identified as the formative stage of filial attachment in rats. The new study, in collaboration with Stephen Rayport’s lab at Columbia, identified MDOBs in neonatal mice and showed that mice lacking the gene for phosphate activated glutaminase, (an enzyme that is key to the function of the neurotransmitter glutamate), have MDOB deficits, the severity of which are a function of the gene dose. i.e., heterozygotes have a mild deficit and survive, whereas homozygotes (knockouts) have severe deficits and do not survive past 2 days. This study establishes the cross-species generality of MDOBs, genetic and neurochemical links to their development, and suggests their functional importance.
Mark Ansorge

The Sackler funding has provided valuable resources to support our research examining the effect of developmental serotonin transporter blockade on behavior, physiology and anatomy. We will present some of our new results at this year’s society of neuroscience meeting and currently prepare a manuscript for submission to the journal “Neuropsychopharmacology”. In addition, of the two RO1 applications that were based on work supported by this Sackler grant, one got funded this spring.

The second year of the Sackler Award has allowed me to further establish a career path in one of the most competitive and interesting areas of developmental psychobiology. Moreover, our work has inspired several collaborations (among them the Sackler laboratory in Glasgow) with researchers in both the clinical and preclinical realms that will bring additional interest to these important developmental questions.

Progress towards developing an inducible SERT knockout mouse.

We have generated mice that express the tetracycline transactivator protein (tTA) under the control of the SERT (serotonin transporter) promoter using a knock-in strategy. This knock-in mutation inactivates the endogenous SERT gene. The tTA in the SERT locus drives expression of genes under the control of the tetO minimal promoter with raphe-specific patterns of expression.

Progress towards determining the specificity of SERT disruption to produce altered adult affective behavior.

We generated postnatal fluoxetine treated mice, with X being saline (control), fluoxetine, citalopram (an SSRI), clomipramine (a tricyclic with SSRI activity) and desipramine (an anti-depressant without SSRI activity). Following weaning and maturation, the mice were tested as adults in the following behavioral paradigms: open field, elevated plus maze, novelty suppressed feeding test (NSF), novelty induced hypophagia test (NIH), and shock escape test. In summary, early postnatal exposure to FLX and clomipramine altered adult behavior in all behavioral tests examined. Postnatal citalopram and desipramine treatment on the other hand had no or only very weak effects on the adult behaviors investigated.

This experiment achieved 3 important points: (a) We replicated the effects of postnatal fluoxetine treatment in an independent group of mice, with an independent batch of drugs and an in part independent group of experimenters. (b) We added another behavioral paradigm, novelty-induced hypophagia, which is sensitive to chronic but not acute antidepressant treatment, and found a robust effect of postnatal treatment. (c) We created a dataset that allows us to compare the effects of various antidepressant drugs. Our hypothesis at the moment is that the effect sizes of treatment depend on the affinity of the drugs towards the SERT, their half-life and the regimen of administration.
We are currently measuring drug levels in the serum and the brain of P4-21 treated mice on P21 and P22. Results from this experiment will allow us to better estimate the level of SERT blockade achieved by the various treatments and test our hypothesis. Although speculative, our preclinical data have the potential to inform clinical trials and practice: at the moment we would conclude that it is safer for pregnant depressed women to use NRIs as opposed to SSRIs.

**SERT inhibition during development leads to a loss in behavioral response to chronic SSRI and NRI treatment in adult mice.**

Last year we performed a study investigating whether SERT (knockout) mice respond to antidepressant treatment. Our results showed that SERT KO mice are behaviorally insensitive to acute and chronic fluoxetine FLX treatment and chronic desipramine treatment (Poster presentation at the NYAS PTSD conference, 2005).

The conclusion from this experiment was that

a) SERTs need to be present in order for SSRIs and NRIs (nor-epinephrine receptor inhibitors) to elicit their antidepressant effects.

b) Loss of SERT function during development rewires the brain in a way so that mice do not behaviorally respond to antidepressant treatment with SSRIs or NRIs, even if the SERT would be present.

The latter hypothesis is supported by clinical data showing that individuals carrying the low expressing SERT allele do not respond to SSRIs as well as individuals carrying the high expressing SERT allele. In order to test hypothesis b) we created a cohort of PN-post-natal control Veh and PN-FLX treated mice and tested their response to acute and/or chronic FLX and desipramine treatment during adulthood. Data of the chronic part of the experiment have been analyzed and strongly support hypothesis b): PN-FLX mice had higher baseline depression-like behavioral levels when compared to PN-Veh mice and did not respond to chronic FLX or desipramine treatment in the NSF and the NIH tests. In a control experiment we could show that PN-FLX mice do respond to diazepam treatment in the NSF test. These data further strengthen the notion that our early postnatal SERT inhibition protocol mechanistically mimics the human low expressing SERT allele phenotype and thus warrants further investigation into the mechanistic basis of this phenotype.

**Progress towards determining the mechanisms underlying the effect of postnatal SERT disruption on adult behavior.**

Last year we found no effect of constitutive genetic SERT disruption on the size or composition of catecholaminergic nuclei (substantia nigra, ventral tegmental area, locus coeruleus), suggesting that the effect of constitutive genetic SERT disruption on raphé composition is rather specific.

Stereological analysis of the dorsal raphé nucleus in PN-FLX treated mice revealed no difference when compared to PN-Veh treated mice. This suggests that the reduced number of serotonergic cells in SERT KO mice is not necessary to mediate the high depression phenotype in those mice.

This result lead us to put the gene chip experiment on hold and use other less expensive techniques first in order to find an anatomical substrate that could potentially mediate the behavioral effects of developmental SERT blockade. We performed two main experiments:
a) Golgi staining of SERT KO and WT mice as well as PN-FLX and PN-Veh mice. All brains are being processed at the moment and analysis will start in October. We will analyze the areas we had proposed for the gene chip experiment.

b) Extra-cellular recordings of serotonergic neurons in the dorsal raphe nucleus of anesthetized PN-FLX and PN-Veh treated mice. Data need to be analyzed. Preliminary results indicate an effect of treatment with developmental SERT blockade resulting in reduced firing rates.

Once we have solid data supporting certain candidate structures we will pursue our proposed genechip study.

**Publications** – see page 12

**Abstracts**


Morelli E, Ansorge MS, Gingrich JA (2006) The effect of developmental exposure to fluoxetine, citalopram, clomipramine and desipramine on adult emotional behavior in mice. SfN.

**Grant Support** – see p. 15

Dr. Raymond Stark – Addendum

1) Progress report for baboon serotonin project:

During infusion of fluoxetine (10mg/d) to pregnant baboons, maternal and fetal concentrations became stable within 24 h at levels comparable to the low therapeutic range in human adults. At steady-state, fetal fluoxetine and norfluoxetine concentrations are almost half those in the mother. This suggests metabolism of both fluoxetine and norfluoxetine by the fetus. Incubation of fetal tissue homogenates with fluoxetine leads to the production of a glucuronide metabolite of the drug suggesting that glucuronidation may be the metabolic process leading to the lower levels of fluoxetine in the fetus during maternal infusion. During fetal infusion, total fetal fluoxetine clearance was 174 ml/min which is higher than other drugs we have studied. These data led to our hypotheses and NIH R-21 funding of SSRI research described below
While most attention has been directed toward the effect of SSRI on the developing nervous system, indirect effects on placental serotonin transport may also occur. In preliminary PET studies, our goal was to image the serotonin transporter in the fetal brain using a C-11 DASB ligand and determine if it were blocked with maternal administration of fluoxetine. The images PET images standardized to dose showed marked intensity overlying placenta and near complete block after maternal fluoxetine administration. These data support the application of PET techniques to study effects of chronic fetal exposure to neuroactive drugs.

2) The absence of anatomic teratogenicity has suggested to some clinicians that SSRIs are the safest therapeutic agents currently available.

However, SSRI use during pregnancy is linked with neurobehavioral disturbances in newborn infants while cessation of SSRI therapy in pregnancy is associated with relapse. Hence, we suggest a pharmacologic strategy to ameliorate these divergent risks, minimize exposure of the fetus to SSRI while providing effective therapy for the mother. Our studies have shown that drug metabolism by the fetus can significantly reduce fetal drug concentrations below those in the mother. We contend that a clear understanding of the capacity of the fetus to metabolize SSRIs will make possible clinical decisions to exploit known characteristics of individual SSRIs and reduce the level of fetal exposure to active agent. Research to define biomarkers of fetal drug exposure will substantiate which antidepressant drugs, based on fetal metabolic profiles, present the least risk to the fetus.

The objective of our R-21 is to provide proof of principle that the metabolism of individual SSRIs affects fetal concentrations of active drug and to develop fetal biomarkers of the effect of the drug and active metabolites. Our central hypothesis is that SSRIs that undergo metabolism by the fetus will have lower drug and higher metabolite levels n the fetus compared to the mother. The effect on fetal physiology will be a function of the combined concentrations of the active agents whether drug or metabolite. The research is pursued with 2 aims: First, we will study two SSRIs in prevalent use, fluoxetine and sertraline, which have distinct metabolic profiles. The approach used will quantify and compare fetal metabolism and placental clearance of drugs in chronic studies of the fetal baboon and correlate metabolism with enzyme activity in the fetal liver. Metabolism in vivo is expected to reflect the developmental expression of the drug metabolizing enzymes. These differences in the metabolic profiles will provide a distinct pattern of fetal exposure to each agent. Secondly, we will correlate changes in parameters of autonomic regulation (heart rate variability), EEG activation (spectral power in frequency bands), cortical synchrony (EEG coherence) and periodic behaviors (fetal state, circadian processes) before during and after exposure with the concentration of active agent in the fetus. We expect dose response profiles will identify specific biomarkers of acute fetal exposure to and withdrawal from SSRI activity.

Collectively, results will provide basic information (dose kinetics, estimates of physiological variance, effects etc.) necessary to mount an in depth investigation of chronic exposure to SSRIs during primate pregnancy and their neurodevelopmental effects on the fetus. Ultimately, with this knowledge, pregnant women and their physicians should be in a better position to make realistic risk-benefit assessments when considering SSRI therapy versus the consequence of untreated major depressive illness in pregnancy.