

## **Developmental Psychobiology**

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### **Overview**

Research in the Department of Developmental Psychobiology 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 who are interested in understanding how natural events and stressful experiences interact with genetic mechanisms to shape the course of normal and abnormal development. The motivation for this work is 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. Studies involving human subjects examine the role of pre- and post-natal experiences on fetal, infant, and child behavior and physiology. 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.

### **Current Research**

A number of ongoing studies in the department were prompted by findings from Dr. Gingrich's laboratory which demonstrated that, contrary to expectations, when mice are not able to express the serotonin reuptake transporter, either by means of genetic engineering or pharmacologic blockade during infancy, as adults they exhibit increased anxiety and depressive-like behavioral traits. Based on these findings, a multidisciplinary initiative was funded by the Sackler Institute to investigate the critical role of serotonin regulation during early development on shaping adult behavior. Phase I of these projects involved collaborations among many members of the department along with Myrna Weissman (Clinical Genetic Epidemiology), Brad Peterson (Child Psychiatry), and Raymond Stark and Marianne Garland (Pediatrics).

Many of the animal studies in the department continue to focus on models designed to help us understand the developmental origins of normal and abnormal expression of fear and anxiety, and the relationship of these affective states to early social bonding and attachment. Dr. Brunelli has recently completed a study showing that selective breeding of rats for extremes in infant anxiety has produced, in adulthood, dramatic differences in genes regulating the hypothalamic/pituitary axis. Dr. Polan continues his 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, and genes that regulate the differentiation of interneurons. He is also examining the interactions of these genes with early environmental stress.

Working with Drs. Muller, Myers, and Moore (Lieber Center), Dr. Shair 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. Further understanding of how the expression of fear is regulated during early development was provided by an important study by Dr. Wiedenmayer who found that that the amygdala mediates fear-related behavior in infant rats.

Dr. Barr has utilized microarray gene expression to define specific patterns of changes in gene expression associated with specific types of painful experiences and in neurons damaged by spinal cord injury. Using a similar large scale assessment of gene expression, Dr. Myers has show that profiles of gene expression in the placenta provide early markers for both over and under feeding as well as exposure to drugs and alcohol.

The role of serotonin in modulating behavioral inhibition was the subject of a 2006 Science article by Dr. Gingrich and his laboratory. They found that serotonin acts via 5-HT<sub>2A</sub> receptors in the cortex to increase “anxiety-related” states in mice. This observation has important implications for the role of higher brain processes in anxiety states. This study has led to the development of translational initiatives with the Division of Anxiety Disorders.

Dr. Welch, who recently joined the department, is exploring the biological mechanisms of nurture and testing new treatments for developmental, behavioral disorders and inflammatory disorders. She recently formed a collaboration with Michael Gershon in the Department of Pathology and Cell Biology that is known as the BrainGut Initiative. The Initiative will further investigate mechanisms activated by nurture that condition the brain-gut axis and influence behavior. New studies build on prior collaborative animal research that was done with David Ruggiero (Neuroscience) demonstrating for the first time that the gut peptide secretin is synthesized in the forebrain by the hypothalamus and demonstrating that chronic GI inflammation activates brain patterns in areas known to be abnormal in autism. Current research is testing the hypothesis that gastrointestinal inflammation and concomitant brain effects may be effectively treated with combined secretin and oxytocin in acquired and congenital/genetic rodent models of colitis.

The department also has an active research program involving human subjects. In one area, Dr. Schechter is pioneering investigations of how interpersonal violent trauma subsequently affects the ways mothers interact with their toddlers and preschoolers. This year he found that PTSD-afflicted mothers' behavior in the lab and at home (i.e. viewing preference for violent media with concomitant child exposure) was markedly atypical compared to that of non-PTSD controls. Similarly, he found significant differences regarding important physiologic correlates to maternal behavior. Other members of the department also examine mother/infant interactions but focus on even younger infants. Dr. Monk has expanded her studies of effects of maternal anxiety, depression, and behavioral and SSRI treatments on neurobehavioral traits of the fetus and newborn. In addition, Drs. Fifer and Myers continue to investigate risk factors for expression of abnormal neurobehavioral outcomes and have now received Phase II funding for a collaborative effort to study 12,000 infants in populations from the Northern Plains in the US and Cape Town, South Africa that are at high risk of exposure to alcohol and nicotine during gestation.

### **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 MD and PhD 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.

### **Awards/Honors**

Dr. Gingrich was the recipient of the Roche-Nature Medicine Prize for Translational Medicine.

Dr. Gingrich was selected to help plan the NIH Blueprint for the year of "Neurodevelopment" in the section of Neurodevelopment and Disease.

Dr. Gingrich was selected to be the new director of the Frontier Fund. The Frontier Fund provides up to \$60,000 per year to young investigators in the Columbia and NYSPI research community.

Dr. Gingrich was awarded one of the first Gatsby Awards for identifying underlying circuitry of specific behaviors.

Drs. Fifer and Myers received a MERIT award from NIH for their grant investigating at-risk populations for neurobehavioral disorders.

Drs. Myers and Fifer were recipients of the 2006 Research Award at the Annual Windflower Ball of the First Candle Foundation for their research efforts on Sudden Infant Death Syndrome.

Dr. Schechter was re-appointed to a third term on the Infant and Preschool Committee of the American Academy of Child and Adolescent Psychiatry (AACAP)/

Dr. Shair served as a guest editor of a special edition in the journal of Developmental Psychobiology, "In Recognition of Myron A. Hofer."

### **New Grants**

Barr, Gordon, Amygdala Gene Expression: Learning in a Sensitive Period  
NINS (RO1)

Barr, Gordon, Gene expression after acute and chronic injury and rescue  
NYS (RO1 equivalent)

Brunelli, Susan, Testing Anxiolytic Compounds in Infant Rats Selectively Bred for High Rates of Ultrasonic Vocalization  
EPIX Corporation

Fifer, William, Perinatal Assessment of At-Risk Infants  
NICHD (R37)

Fifer, William and Myers, Michael, Prenatal Alcohol in Sudden Infant Death Syndrome and Stillbirth (PASS) Network NICHD (U01))

Fifer, William, Center for Health Research with Tribes in SD-MT-WY. Project IV, Early predictors of Adverse Neurobehavioral Outcomes in Young Children"  
NICHD (sub-contract of P20: U. South Dakota)

Gingrich, Jay, Gene-Environment Interactions in 5-HTT Deficient Mice  
NIMH (RO1)

Gingrich, Jay, Role of Cortical 5-HT<sub>2A</sub> Receptor Signaling in Psychosis  
Gatsby Foundation

Shair, Harry, Formation of Infant/Father Social Relationships: Mechanisms and Modulators NIMH (R21)

Welch, Martha, Brain Gut Initiative, Private Funding

Wiedenmayer, Christoph, Fear memory formation in early life  
NIMH (R21)

Wiedenmayer, Christoph, The prefrontal cortex: responses to threat in early life  
NIMH (RO1)

### **Publications**

Bamat NA, Brunelli SA, Kron MM, Schulte AR, Zimmerberg B. Behavioral effects of toluene in rats selectively bred for infantile vocalization rate. *Neurotoxicol Teratol.* 2005, 27:883-90.

Barr GA, Gao P, Wang S, Cheng J, Qin J, Sibille EL, Pavlidis P. Microarray analysis of gene expression following the formalin test in the infant rat. *Pain.* 2005, 117:6-18.

Barr, G.A., Gao, P. Wang, S., Cheng, J. Qin, J., Sibille, E. and Pavlidis, P. Developmental changes in gene expression induced by injury in the rat. *Pain*, 2005, 117:6-18.

Brunelli SA, Nie R, Whipple C, Winiger V, Hofer MA, Zimmerberg B. The effects of selective breeding for infant ultrasonic vocalizations on play behavior in juvenile rats. *Physiol Behav.* 2006, 87:527-36.

Brunelli SA. Development and evolution of hidden regulators: selective breeding for an infantile phenotype. *Dev Psychobiol.* 2005, 47:243-52.

Butkevich IP, Barr GA, Mikhailenko VA, Otellin VA. Increased formalin-induced pain and expression of fos neurons in the lumbar spinal cord of prenatally stressed infant rats. *Neurosci Lett.* 2006, 403:222-6.

Chen SW, Shemyakin A, Wiedenmayer CP. The role of the amygdala and olfaction in unconditioned fear in developing rats. *J Neurosci.* 2006, 26:233-40.

Coates SW, Schechter DS. Preschoolers' posttraumatic stress post-9/11. In C Wachs, L Jacobs (Eds.) *Parent-Focused Child Therapy: Attachment, Identification, and Reflective Function.* New York: Rowman & Littlefield, Inc. pp. 93-110, 2006.

Etkin A, Pittenger C, Polan HJ, Kandel ER. Toward a neurobiology of psychotherapy: basic science and clinical applications. *J Neuropsychiatry Clin Neurosci.* 2005, 17:145-58.

Fifer WP, Grieve PG, Grose-Fifer J, Isler JR, Byrd D. High-density electroencephalogram monitoring in the neonate. *Clin Perinatol.* 2006, 33:679-91.

Fifer WP, Myers MM, Sahni R, Ohira-Kist K, Kashyap S, Stark RI, Schulze KF. Interactions between sleeping position and feeding on cardiorespiratory activity in preterm infants. *Dev Psychobiol.* 2005, 47:288-96.

Frye CA, Sumida K, Zimmerberg B, Brunelli SA. Rats bred for high versus low anxiety responses neonatally demonstrate increases in lordosis, pacing behavior, and midbrain 3 alpha, 5 alpha-THP levels as adults. *Behav Neurosci.* 2006, 120:281-9.

Gingrich JA. Oxidative stress is the new stress. *Nat Med.* 2005, 11:1281-2.

Grieve PG, Myers MM, Stark RI, Housman S, Fifer WP. Topographic localization of electrocortical activation in newborn and two- to four-month-old infants in response to head-up tilting. *Acta Paediatr.* 2005, 94:1756-63.

Hennessy MB, Miller EE, Shair HN. Brief exposure to the biological mother potentiates the isolation behavior of precocial Guinea pig pups. *Dev Psychobiol.* 2006, 48:653-659.

Hofer, M. A. (2006). Psychobiological Roots of Early Attachment. *Current Directions in Psychological Science*, 2006, 15, 84-88.

Kellendonk C, Simpson EH, Polan HJ, Malleret G, Vronskaya S, Winiger V, Moore H, Kandel ER. Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron.* 2006, 49:603-15.

Kinney HC, Myers MM, Belliveau RA, Randall LL, Trachtenberg FL, Fingers ST, Youngman M, Habbe D, Fifer WP. Subtle autonomic and respiratory dysfunction in sudden infant death syndrome associated with serotonergic brainstem abnormalities: a case report. *J Neuropathol Exp Neurol.* 2005, 64:689-94.

Kuba T, Wu HB, Nazarian A, Festa ED, Barr GA, Jenab S, Inturrisi CE, Quinones-Jenab V. Estradiol and progesterone differentially regulate formalin-induced nociception in ovariectomized female rats. *Horm Behav.* 2006, 49:441-9.

Muller JM, Brunelli SA, Moore H, Myers MM, Shair HN. Maternally modulated infant separation responses are regulated by D2-family dopamine receptors. *Behav Neurosci.* 2005, 119:1384-8.

Myers MM, Gomez-Gribben E, Smith KS, Tseng A, Fifer WP. Developmental changes in infant heart rate responses to head-up tilting. *Acta Paediatr.* 2006, 95:77-81.

Myers MM, Shair HN, Cohen M. Blood pressure responses to feeding in infancy: spin-offs of serendipity. *Dev Psychobiol.* 2005, 47:268-77.

Polan HJ. Guidance and differentiation of maternally directed orienting behaviors: probing the origins of filial attachment. *Dev Psychobiol.* 2005, 47:278-87.

Schechter DS, Coates SW. Relationally and Developmentally Focused Interventions with Young Children and Their Caregivers Affected by the Events of 9/11. In Y. Neria, R. Gross, R. Marshall, E. Susser (Eds.) *September 11, 2001: Treatment, Research and Public Mental Health in the Wake of a Terrorist Attack*, New York: Cambridge University Press. pp. 402-427, 2006.

Schechter DS, Coots T, Zeanah CH, Davies M, Coates SW, Trabka KA, Marshall RD, Liebowitz MR, Myers MM. Maternal mental representations of the child in an inner-city

clinical sample: violence-related posttraumatic stress and reflective functioning. *Attach Hum Dev.* 2005, 7:313-31.

Villalobos C, Beique JC, Gingrich JA, Andrade R. Serotonergic regulation of calcium-activated potassium currents in rodent prefrontal cortex. *Eur J Neurosci.* 2005, 22:1120-6.

Weisstaub NV, Zhou M, Lira A, Lambe E, Gonzalez-Maeso J, Hornung JP, Sibille E, Underwood M, Itohara S, Dauer WT, Ansorge MS, Morelli E, Mann JJ, Toth M, Aghajanian G, Sealson SC, Hen R, Gingrich JA. Cortical 5-HT<sub>2A</sub> receptor signaling modulates anxiety-like behaviors in mice. *Science.* 2006, 313:536-40.

Welch M.G., R.S. Northrup, T.B. Welch-Horan, R.J. Ludwig, C.A. Austin, and J.S. Jacobson. Prolonged Parent-Child Embrace Therapy among 102 Children with Behavioral Disorders: Outcomes and Underlying Mechanisms. *Compl Ther in Clin Practise* 2006,12:3-12

Welch MG and Ruggiero DA. Chapter 7. GABA in autism and related disorders, Predicted therapeutic role of secretin and oxytocin in autism: Implications for treatment of mental illness, *International Review of Neurobiology*, Elsevier; 2005.

Welch MG, Ludwig RJ, Opler MG, Ruggiero DA. Secretin's role in the cerebellum: A larger biological context and implications for developmental disorders. *Cerebellum*, 2006, 5:2-6.

Welch MG, Welch-Horan TB, Anwar M, Anwar N, Ludwig RJ, Ruggiero DA. Brain effects of chronic IBD in areas abnormal in autism and treatment by single neuropeptides secretin and oxytocin. *J Mol Neurosci* 2005, 25:259-274.

Wiedenmayer CP, Bansal R, Anderson GM, Zhu H, Amat J, Whiteman R, Peterson BS. Cortisol levels and hippocampus volumes in healthy preadolescent children. *Biol Psychiatry.* 2006, 60:856-61.