

The Sackler Institute for Developmental Psychobiology
Weill Cornell Medical College
Annual Report for June 2009-May 2010

The Institute continues to excel in vertically integrated translational approaches from human imaging to mouse genetics across development. The faculty and fellows have received numerous awards (see *Grants and Awards*) and training remains a priority with the continuation of the Summer Institute on the Biology of Developmental Disabilities and involvement in medical and graduate training (see *Education, Training and Outreach*). This year over 50 papers were either accepted or published, a few of which are highlighted below (see *Program of Research and Publications*). Finally, new scientific initiatives of The Institute are described in *Future Directions*.

Academic Faculty and Staff

Sackler Faculty

Dima Amso, Ph.D., Assistant Professor of Psychology in Psychiatry
B.J. Casey, Ph.D., Director and Sackler Professor of Developmental Psychobiology
Barbara Finlay, Ph.D., Visiting Professor of Psychology in Psychiatry, Cornell
Michael Posner, Ph.D., Professor of Psychology in Psychiatry, Emeritus, Oregon
James Swanson, Ph.D., Part-time Professor of Psychology in Psychiatry, UCI
Nim Tottenham, Ph.D., Adjunct Assistant Professor of Psychology in Psychiatry, UCLA
Jason Zevin, Ph.D., Assistant Professor of Psychology in Psychiatry

Sackler Staff

Deanne Lamb, Institute Administrator
Jae Woo, M.D., IT Manager

Sackler Research Assistants

Juli Dolzhenko, Research Assistant
Nicholas Franklin, Research Assistant
Patrick Harvey, Research Assistant
Eva Hulse, Research Coordinator
Brian Kramer, Research Assistant
Victoria Libby, Research Assistant
Erika Ruberry, Research Assistant

Sackler Predoctoral and Postdoctoral Fellows

Kat Agres, Joint Cornell-Weill Ph.D. Candidate
Hia Datta, Ph.D., Postdoctoral Fellow
Stephanie Duhoux, Ph.D., Postdoctoral Fellow
Lauren Emberson, Joint Cornell-Weill Ph.D. Candidate
Michael Frank, Visiting Sackler Fellow, MIT Ph.D. candidate
Helena Frielingsdorf, M.D., Ph.D., Postdoctoral Fellow
Rebecca Jones, Neuroscience Ph.D. student
Matthew Malter-Cohen, Neuroscience Ph.D. student
Jeremy Skipper, Ph.D., Postdoctoral Fellow
Fatima Soliman, Tri-Institutional M.D.-Ph.D. student
Leah Somerville, Ph.D., Postdoctoral Fellow

Distinguished Sackler Network Scholars

Oana Benga, Ph.D., Babes-Bolyai University, Romania

Sarah Durston, Ph.D., University of Utrecht, The Netherlands

Annette Karmiloff-Smith, Ph.D., University College London, United Kingdom

Urs Maurer, Ph.D., Swiss National Science Foundation, Switzerland

Bruce D. McCandliss, Ph.D., Vanderbilt University, Tennessee, United States

Gaia Scerif, Ph.D., University of Oxford, United Kingdom

Program of Research

This year, several empirical studies have been completed and published in high profile journals (*Science*, *PNAS*) using the techniques of brain imaging, human and mouse genetics, electrophysiology, eye tracking and behavioral methods, to study typical and atypical populations from childhood to adulthood (see *Publications*). Below are highlights from a few studies representing three general domains of study: 1) learning and development; 2) genomics; and 3) mental illness and health.

Studies of Learning and Development

Behavioral and imaging studies of learning and development form the very foundation of the Institute's research program and lay the critical groundwork for our genetic and clinical studies. Therefore we highlight only a few of these studies across the domains of perception, attention, language and social development.

Statistical Learning in Infants and Children. Dr. Dima Amso is examining the neural basis of habituation and novelty preferences in infants and children using eye-tracking and brain imaging methods. This work uses an elegant paradigm across ages to dissociate different learning systems and lays the groundwork for identification of learning disabilities early in life; this forms the basis of Dr. Amso's NIMH K-award.

Attention, Perceptual and Object Learning in Infants. Saccades early in infancy are largely reflexive, with voluntary attention-directed eye movements emerging at approximately three to four months of age. In a series of infant studies, Dr. Amso is investigating the mechanisms of the development of visual selection. Her work suggests that where infants look determines what they perceive and is dependent on their ability to control their eye movements. In related work, she is using electrophysiological measures to constrain current developmental theory on how infants can use repetition to learn to organize their environment.

Social Learning in Infancy. The ability to discriminate emotional expressions in others' faces is a key component of normal social interaction. A first step in this process is the ability to discern *perceptual* differences between faces and to generalize the encoded emotion across individuals. Drs. Nim Tottenham and Amso are examining how individual differences in information gathering, via shifts of eye gaze, support infants' ability to discriminate between emotional expressions. This work provides a developmental framework for examining face processing deficits in developmental disorders.

Speech Perception and Development. Understanding how non-native speakers compensate for atypical speech sound processing may provide the basis for novel remediation strategies for communication disorders. Dr. Jason Zevin, in collaboration with Dr. Bruce McCandliss at Vanderbilt, is examining the neural basis of language development, with a specific focus on the development of speech perception in American and Japanese native speakers. They have completed a new eye-tracking study with adult natives from the US and Japan. This work serves as the basis of a recently submitted NIH grant by Dr. Zevin.

Importance of Context in Spoken Communication. Spoken communication is accompanied by a wealth of contextual information and knowledge or expectations of the listener. Most neurobiological research on speech perception discards context in favor of studying isolated speech sounds or words. Dr. Jeremy Skipper under the mentorship of Dr. Jason Zevin, is examining the neural mechanisms of language comprehension in real-world settings, where the brain can make use of context to aid in communication. This work is the basis of a funded NIH K99 grant application (PI: Skipper).

Genomic Investigations

The Sackler Institute is rapidly establishing a high profile in genomic research translating transgenic mouse models to human behavior and disease. These genomic studies were made possible by generous gifts to the Sackler Institutes in the U.S. and a recent NIMH center grant. Several recent findings are highlighted below on brain-derived neurotrophic factor (BDNF) and the serotonin transporter (SERT).

BDNF Genotype and Extinction of Fear Memories. A core problem in many individuals with anxiety and depression is difficulty learning what cues and settings signal safety or danger and unlearning such associations when they no longer exist. M.D.-Ph.D. student Fatima Soliman, under the mentorship of Drs. B.J. Casey and Francis Lee, developed a paradigm for examining the impact of brain-derived neurotrophic factor (BDNF) on these forms of learning with fMRI and psychophysiological responses in humans and freezing behavior in mice. They recently reported in *Science* that the BDNF Val66Met polymorphism results in slower extinction of a fear memory. The findings have significant implications for exposure therapies that rely on principles of extinction learning, which are routinely used with patients with anxiety disorders (e.g. PTSD and phobias).

BDNF and Cumulative Risk Factors Relate to Symptoms of Anxiety. Medical student, Ben Angarita, in collaboration with Dr. Casey and Dr. Charles Glatt, examined the influence of BDNF Val66Met and early psychosocial stressors on symptoms of anxiety. Preliminary results from a sample of nearly 100 individuals suggest a greater number of early psychosocial risk factors are needed to produce a high amount of anxiety in the individuals without, compared to those with, the polymorphism. This work was presented at the annual AACAPP meeting.

Function of SERT Gene (rs3813034). The human gene for SERT contains a very unusual feature: a somatic deletion. This somatic deletion is distinct from the highly studied serotonin transporter-linked polymorphic region (5HTTLPR), which is a common regulatory polymorphism in the SERT gene (*SLC6A4*). Currently Dr. Glatt is examining the functional effects of the somatic deletion on expression of SERT to elucidate the regulation of mood and behavior and potential risk for behavioral disorders. Understanding the functional properties of the somatic deletion might also help clarify the inconsistent associations of the 5HTTLPR with behavioral disorders and behavior – a topic of growing interest in psychiatric genetics. This work is part of a pending NIH R21 application.

SERT (rs3813034) and Panic Disorder. Genetic markers in the serotonin transporter have been associated with panic disorder. The associated polymorphisms do not include the serotonin transporter-linked polymorphic region and show no obvious functional attributes. A common polymorphism (rs3813034) that occurs in one of the two reported polyadenylation signals for the serotonin transporter and is in linkage disequilibrium with the panic disorder-associated markers. In a collaboration across the N.Y. Sackler Institutes, Dr. Glatt and Dr. Myrna Weisman tested whether rs3813034 might be the risk factor that explains the association of the serotonin transporter and panic disorder in a sample of over 300 patients and over 540 controls with similar population structure. Association testing of rs3813034 in panic disorder identified a significant association with a relative risk of 1.56 and 1.81 for the heterozygous and homozygous variant genotypes, respectively. These findings suggest that rs3813034 is a putative risk factor for panic disorder and other behavioral disorders that involve dysregulation of serotonergic neurotransmission. These findings were recently published in *Biological Psychiatry*.

SERT (rs3813034) and Fear Extinction Retention. Drs. Glatt and Casey in collaboration with PhD student Cate Hartley and Dr. Liz Phelps of NYU are exploring whether two polymorphisms tied to variation in 5-HTT expression are associated with differences in extinction retention. Using a two-day fear conditioning paradigm of acquisition and the initial extinction phase, followed by day two of a second extinction phase, they show that the polyadenylation polymorphism in the serotonin transporter (rs3813034) is associated with individual variation in extinction retention, as well as trait anxiety and depressive symptoms, while the serotonin transporter-linked promoter region (5HTTLPR) was not associated with these measures. These results suggest that genetically-mediated differences in extinction retention may be associated with risk of developing anxiety disorders.

Studies of Mental Illness and Health

The overarching objective of the Institute is to delineate the biological mechanisms underlying mental health and illness, and to direct treatments and interventions with the goal of ameliorating mental illness in the future. The studies currently underway focus on risk factors related to anxiety, depression and addiction. These studies are moving the field toward preventive and personalized medicine.

Brain Development and Function Following Institutionalization. The long-term outcomes of children reared in orphanages abroad has become a primary health concern given the rising number of adoptions of these children to the United States. Drs. Casey and Tottenham have been exploring the effects of prior institutionalization on brain and socioemotional development using magnetic resonance imaging (MRI). The findings suggest long-term alteration in amygdala structure and function that is related to the amount of eye contact they have with their parents when interacting. Current investigations focus on the functional significance of these anatomical changes and on the genetic contributions to these phenotypes following stress. This work was funded by a NIMH R01 and recently published in *Developmental Science* (Tottenham et al., 2009; in press), receiving the journal's *Early Career Research Prize*.

Biobehavioral Markers for Anxiety Disorders. Childhood anxiety disorders are a prevalent public health issue affecting as many as one in ten children and increasing risk for psychiatric disorders throughout the lifespan. Dr. Leah Somerville, a postdoctoral fellow working with Dr. Casey, has developed a paradigm to delineate brain systems critical to symptoms of anxiety across development and provide preliminary evidence for their role in anxiety disorders and their predictive merit for risk in familial cases. Ultimately this work should provide biologically valid behavioral markers of risk for anxiety disorders that will facilitate early identification and prevention as well as new outcome measures for clinical trials for optimizing personalized treatment. This work is part of a pending NIMH K99 application.

Effects of Psychological Stress on Prefrontal Cortex. Conor Liston, M.D., Ph.D., now a psychiatry resident at Weill Cornell Medical College and a prior recipient of the Soros and Perry Awards, examined in humans and animals the impact of moderate stress in collaboration with Dr. Casey and Dr. Bruce McEwen of The Rockefeller University. Both species show changes in attention shifts, but not behavioral set shifting, following stress, which normalizes once the stressor is removed. Human imaging and animal histological studies show changes in prefrontal cortical regions that support attention shifting (see Liston, McEwen & Casey, 2009).

Effects of Peer Interaction on Behavior. Rebecca Jones, a Neuroscience Ph.D. student, together with Drs. Somerville and Casey, is using a task that parallels human and nonhuman primate studies of reinforcement learning to determine how peers can act as secondary reinforcers to bias behavior, and examines the neural correlates with fMRI. Preliminary results suggest that individuals are faster to respond to a peer who has interacted with them relative to one who has not interacted with them as much. These behavioral changes are paralleled by changes in reward-related circuitry implicated in primary reinforcement and addiction.

Development of Appetitive Behavior. Adolescent risk-taking is a public health issue that increases the odds of poor lifetime outcomes. One factor thought to influence adolescents' propensity for risk-taking is an enhanced sensitivity to appetitive cues, relative to an immature capacity to exert sufficient cognitive control. Drs. Casey and Somerville together with Dr. Todd Hare of Cal Tech have tested this hypothesis by characterizing interactions among subcortical and cortical regions during an impulse control task with varying appetitive load using fMRI. Child, adolescent, and adult participants performed the task with appetitive and neutral cues. Task performance to neutral cues showed steady improvement with age. However, on trials for which the individual had to resist approaching appetitive cues, adolescents failed to show the expected age-dependent improvement. This performance decrement during adolescence was paralleled by enhanced activity in the ventral striatum. Prefrontal cortical recruitment correlated with overall accuracy and showed a linear response with age. Taken together, these findings implicate exaggerated ventral striatal representation of appetitive cues in adolescents in the absence of a mature cognitive control response. Biased responding in this system is one possible mechanism underlying heightened risk-taking behavior during adolescence.

Collaborative Studies Relevant to Addiction. Dr. Casey has been working with Dr. Walter Mischel of Columbia University to relate preschoolers' ability to delay gratification with their cognitive control abilities in adolescence. Toddler measures of delay of gratification are associated with substance abuse in adulthood. Preliminary results suggest those individuals most able to wait for a reward as toddlers are better able to resolve conflict on cognitive control tasks as adolescents. A collaborative National Science Foundation grant (PI: Shoda) involving University of Washington, Columbia University, Berkeley, and University of Michigan has been awarded to support this program of research. Preliminary findings are published in *Psychological Science* and are currently being submitted to a special issue of *SCAN*.

Most recently, Casey is collaborating with Dr. Mischel and Dr. Kevin Ochsner of Columbia University on a project relevant for addiction and eating disorders. Together they are using social, cognitive and affective neuroscience approaches to understand the development of neural mechanisms that enable us to regulate the appetitive pull of potentially unhealthy substances (e.g., fattening foods or drugs) and the aversive push of unpleasant emotions that might motivate one to seek these substances in the first place. They are using delay of gratification, appetitive go/nogo and emotion regulation tasks that they have each developed. This work has resulted in a collaborative grant submission to NIH (PI: Ochsner).

Genetic and Imaging Studies of Eating Disorders. Dr. Casey is collaborating on two studies with investigators at NYSPI. The first is a genetic imaging study of obesity in children focusing on the effect of the FTO gene and neural circuitry underlying sensitivity to food cues in children. This work has been submitted as part of a special RFA-initiated RO1 to the NIH and uses behavioral paradigms developed at The Institute. The second is a collaborative study recently funded by the Klarman Foundation to examine neural correlates of delay of gratification, discounting and impulse control in anorexia nervosa with Drs. Tim Walsh and Joanna Steinglass (PI).

Future Directions

The Institute is moving into three new areas of inquiry within the field of child psychiatry. Specifically we are mounting new research programs in the development of novel biomarkers for predicting risk and treatment outcomes for anxiety and affective disorders (generalized anxiety and PTSD), eating disorders (anorexia nervosa and obesity) and addiction. We will use a combination of approaches including: 1) development of genetically modified mice for parallel mouse and human genetic studies for genes implicated in these disorders that involve the neurotrophin, serotonin and endocannabinoid systems; 2) epidemiological studies in international collaborations to examine environmental factors that contribute to these disorders and directly build on the efforts of the NIH National Children's Study; and 3) cross-fostering studies in mice to dissociate genetic and parental influences on neurodevelopment and behavior relevant to these disorders.

These new directions build directly on recent investments by the Psychiatry Department and the NIH, leveraging both internal and external resources for The Institute's mission. First, the department has hired a new head of Child Psychiatry, Dr. John Walkup. His expertise is in treatment and clinical trials of pediatric anxiety and tic disorders. Moving in the direction of pediatric disorders will take full advantage of this hire and integrate basic research within The Institute with clinical investigations within the Division of Child and Adolescent Psychiatry. Second, the department has invested in a significant renovation of the Westchester eating disorders facility and hired a new head of that program, Dr. Evelyn Attia. This investment coincides with NIH announcing several funding opportunities in the area of eating disorders given the epidemic of obesity in children in the US and the high mortality rate in anorexia nervosa. The Institute will take full advantage of these investments to leverage new research programs in these areas. Finally, the NIH has invested in The National Children's Study, one of the largest US-based research studies ever to look at the ways in which the environment and genetics interact to influence child health and development. The Institute has partnered with NIH sponsored initiatives to become involved in this epidemiological study.

Education, Training and Outreach

A significant objective of the Institute is in training, education and outreach. The Institute's network has international collaborations established with Romania, the United Kingdom, Switzerland and The

Netherlands in addition national ones with Cornell, Columbia, Connecticut, NIMH, NYU, University of Oregon, University of Pennsylvania, Princeton, Rockefeller, Stanford, UC Irvine, UCSD, Scripps, University of Hawaii, MGH and Yale. Highlights of the Institute's training and outreach program are provided below.

2010 Summer Institute on the Biology of Developmental Disabilities. Dr. Casey has received funding for a tenth year to direct a week-long course on the biology of developmental disabilities from the John Merck Fund. This year's course is co-directed by BJ Casey of the Sackler Institute and Barbara Finlay of Cornell University and will focus on important developments in evolutionary biology that have direct implications for how we conceptualize the nature and treatment of developmental disorders. (see: <http://www.sacklerinstitute.org/cornell/summerinstitute/2010>).

Developing Researchers in Neuropsychiatric Imaging. The Institute actively participates in summer workshops as part of a NIMH R25 Grant (PI: Casey) to train researchers in neuropsychiatric imaging.

Weill Graduate School of Medical Science. Dr. Casey is the Director of the Neuroscience Program at Weill Graduate School of Medical Science. The program includes over 60 faculty and graduate students. The Institute has taken a significant role in recruitment, teaching and sponsoring student rotations and PhD candidates from the graduate program and from the Tri-Institutional M.D.-Ph.D. program.

Residency Education. Drs. Amso, Casey, and Somerville all played significant roles this year in teaching both adult and child psychiatry residents at Weill Cornell Medical College as part of the Residency program curriculum.

Brain to Mind. Drs. Amso, Casey, Somerville and Zevin all played significant roles this year in teaching medical students at Weill Cornell and Weill Qatar about developmental systems neuroscience. Each faculty member provided lectures and labs for the students that has resulted in participation of the medical students in rotations and Sackler seminars.

Neuron to Brain. Drs. Amso, Casey, Somerville and Zevin all played significant roles this year in teaching Weill Biomedical Graduate Program in Neuroscience related courses that link brain and behavior. Some of the best teaching evaluations were given to this group, with highest praise to Dr. Amso, for her lectures on attention and developmental neuroscience.

Ithaca-Weill Joint Graduate Program in Development and Learning. Dr. Casey in collaboration with Dr. Barbara Finlay of Cornell University-Ithaca has hosted joint campus meetings of psychology and neuroscience faculty for the past three years and have received an NICHD T32 joint institutional interdisciplinary training grant submission for predoctoral fellows in development and learning (see <http://neuroscience.cornell.edu/imagine.html>).

Columbia-Cornell Sackler Institute Meeting. A Cornell-supported symposium, both organized and chaired by Dr. Jason Zevin, was held at the annual Winter Meeting on Developmental Psychobiology, co-directed by Dr. Bill Fifer of the Sackler Institute at Columbia and Dr. Gordon Barr. These meetings have resulted in joint mentorship of fellows and collaborative research studies between the two institutes. The symposium was: "Developmental Processes with Long Tails," which will also be the title of a special issue co-edited with Dr. Kevin Bath (tentative publication date: Jan., 2011). The issue will explore a wide range of developmental phenomena that are most often studied during discrete windows of "interesting" development, and examine how the same mechanisms of developmental change play out over much longer stretches of the lifespan.

Grants and Awards

Grants and Awards (2009-2010)

Dr. Casey received a grant from the John Merck Fund to support the 10th annual Summer Institute on the Biology of Developmental Disabilities that she has been directing for the past eight years. This course exposes students to animal, imaging, genetic, epidemiologic, and computational modeling approaches to understanding learning within typical and atypical development.

Dr. Casey in collaboration with Dr. Barbara Finlay of Cornell University-Ithaca received a NICHD T32 cross-campus interdisciplinary training grant for predoctoral fellows in development and learning. This training program bridges imaging, genetic and clinical approaches from the Medical College together with

computational, behavioral and theoretical approaches from the Ithaca campus in psychology and neuroscience.

Dr. Casey is part of multi-site imaging genomics grant funded by NIDA (RC2 DA029475, PI:Jernigan) to assemble a large, cross-sectional imaging-genomics dataset to be used as a shared resource for investigations of genetic bases of neural phenotypes and age-by-genotype interactions that may represent genetically-mediated differences in developmental trajectories.

Dr. Casey is part of a collaborative study recently funded by the Klarman Foundation to examine neural correlates of delay of gratification, temporal discounting and impulse control in anorexia nervosa with Drs. Tim Walsh and Joanna Steinglass at Columbia (PI).

Dr. Jeremy Skipper received a K99/R00 to investigate neural mechanisms of language comprehension in real-world settings, where the brain can make use of context to aid in communication. His work has shown that spoken communication is accompanied by a wealth of contextual information, yet most neurobiological research on speech perception discards context in favor of studying isolated speech sounds or words.

Dr. Zevin was awarded an NIH R21 grant to study phonetic representation in temporal cortex using novel applications of multivariate analysis techniques. He will use machine learning models to identify patterns of brain activity that correspond to particular speech sound categories. The proposed combination of data collection and analysis techniques has great potential for use in basic, translational and clinical research on the development and plasticity of speech perception as well as communication disorders including dyslexia and language impairment related to deficits in speech sound categorization.

Pending Grants and Awards

Dr. Casey is collaborating with investigators on a genetics imaging study of obesity in children focusing on the effect of the FTO gene and neural circuitry underlying sensitivity to food cues in children. This work has been submitted as part of a special RFA-initiated RO1 to the NIH and uses behavioral paradigms developed at the Institute.

Dr. Casey is collaborating with Drs. Ochsner and Mischel on a NIDA application using social, cognitive and affective neuroscience approaches to understand the development of neural mechanisms that enable us to regulate the appetitive pull of potentially unhealthy substances (e.g. fattening foods or drugs) and the aversive push of unpleasant emotions that might motivate one to seek these substances in the first place.

Dr. Charles Glatt submitted a NIMH R21 to investigate the functional effects a new serotonin transporter polymorphism.

Dr. Leah Somerville submitted a NIH K99/R00 application to examine transient and sustained emotional regulation processes across development.

Dr. Zevin, collaborating with Bruno Tagliaferri (PI), submitted a NIMH R43 application to develop software that will enable researchers to temporally coregister and combine data from multiple modalities in order to realize the long-term goal of studying the brain basis of cognition with multiple, converging methodologies.

Dr. Zevin is collaborating with Ken Pugh (PI) of Haskins Labs on a R01 HD065794 submission to examine neurobiological predictors of spoken and written language learning using multiple imaging methods.

Dr. Zevin is collaborating with Ram Frost (PI) of Haskins Labs on a R01 DC application to examine neurocognitive determinants of second language literacy development in adolescents.

The Institute directly, and in collaboration with others, has grants and awards from NSF, NIMH, NIDA, NIDCD, the Dewitt Wallace Readers Digest, and the John Merck Fund. This funding supplements the generous gifts by the Mortimer D. Sackler, M.D. family.

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