

The Sackler Institute for Developmental Psychobiology
Weill Cornell Medical College
Annual Report for June 2010-May 2011

The Institute continues to maintain a distinguished international reputation in research, training and outreach. The faculty and fellows have received numerous awards (see *Grants and Awards*) and published over 50 scientific papers (see Publications). Training remains a priority with numerous local and international sponsored events (see Training and Education). Outreach activities involving the public range from those related to developmental neuroscience and the law to those linking neuroscience with the arts (see *Outreach Activities*). This report highlights several of the accomplishments of this past year.

Academic Faculty and Staff

Sackler Faculty

B.J. Casey, Ph.D., Director and Sackler Professor of Developmental Psychobiology

Barbara Finlay, Ph.D., Adjunct 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 Affiliated Faculty

Kevin Bath, Ph.D., Instructor

Francis S. Lee, M.D., Ph.D., Associate Professor

Charles E. Glatt, M.D., PhD., Assistant Professor

Sackler Staff

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Patrick Harvey, Research Assistant

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Natasha Mehta, Research Assistant

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Erika Ruberry, Research Assistant

Sackler Predoctoral and Postdoctoral Fellows

Kat Agres, Joint Cornell-Weill Ph.D. Candidate

Hia Datta, Ph.D., Postdoctoral Fellow

Suzanne Dikker, Ph.D., Postdoctoral Fellow

Stephanie Duhoux, Ph.D., Postdoctoral Fellow

Helena Frielingsdorf, M.D., Ph.D., Postdoctoral Fellow

Rebecca Jones, Neuroscience Ph.D. student
Matthew Malter-Cohen, Neuroscience Ph.D. student
Leah Somerville, Ph.D., Postdoctoral Fellow
Theresa Teslovich, Neuroscience Ph.D. student
Chelsea Helion, Joint Cornell-Weill Ph.D. Candidate
Jie Yang, 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 (*Neuron*, *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) human learning and development; 2) translational human and mouse genetics; and 3) mental illness and health.

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 a few of these studies below.

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 published several papers comparing neural responses to native and non-native speech contrasts. 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. 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), and forms the basis of a new proposal to incorporate the role of context into investigations of second language speech perception (PI:Zevin).

Typical and atypical development of the reading circuit across languages. In collaboration with colleagues at Beijing Normal University and Haskins Laboratories, Dr. Jason Zevin is pursuing a program of research that combines computational modeling and functional neuroimaging to study how the reading system develops in response to the demands of different writing systems. The modeling suggests that essentially the same cognitive architecture can be successfully tuned to multiple writing systems, even when they differ dramatically in their surface features. This motivates parallel studies of English and Chinese, in which differential contributions of the same brain regions can be probed using a variety of novel analysis techniques.

Statistical learning with emergent functional units. Most studies of statistical learning use stimuli that are the same from presentation to presentation, or fit into familiar conceptual categories. The implicit assumption is that statistical learning is in some way hierarchical: in order to track co-occurrence statistics across syllables, for example, one must first be able to categorize the syllables reliably. This assumption is inconsistent with many of the situations in which statistical learning could be useful for language learning, especially in infancy, when the categorization abilities for speech sounds are still demonstrably in flux. We have found that adults could learn from sequences of sounds, even when these were defined over physically variable exemplars, drawn from unfamiliar categories. Although this work is in its early stages (the first paper is under review at *Cognition*) it is likely to develop into a key theme in Dr. Zevin's research, because of its potential to address basic questions about how the assays we use to study learning in the lab relate to how learning might work in the more complex, dynamic context of the real world.

Effects of Peer Interaction on Learning and 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 may act as secondary reinforcers to bias behavior. She has shown 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. These findings are under review at *Journal of Neuroscience*. She is in the process of collecting and analyzing data on this imaging task with children and adolescents.

Effects of Reward and Difficulty on Behavior across Development. Adolescents have been shown to be differentially sensitive to rewards relative to children and adults (Somerville et al. 2011). In a NIMH funded study (Casey: PI), we are examining how rewards influence forced choice responses as a function of task difficulty. When participants are rewarded for making one choice (e.g., whether a display of dots is moving left or right), both adults and adolescents are faster to choose the direction that has been rewarded. However, when the choice is difficult (fewer dots moving in the same direction), adolescents are slower to choose the direction that has been rewarded previously, as if to optimize their gains by slowing down their performance to ensure they will be rewarded for an accurate response. These findings suggest that adolescents may work harder for rewards than adults. We are currently examining neural correlates of this developmental pattern with fMRI.

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

behavior 40 years later. Preliminary results suggest that individuals who could not delay gratification at 4 years of age (Low Delayers) had difficulty suppressing responses to “hot” but not “cold” cues forty years later, as compared to High Delayers. The ventrolateral prefrontal cortex was involved in accurately withholding a response, but did not differentiate high and low delay groups. In contrast, the ventral striatum- a region implicated in addictive and reward related behavior- was sensitive to appetitive social cues and differentiated the high and low delayers with low delayers activating this region more. These findings suggest that our ability to resist temptation varies, not only by how well we can control our impulses, but also by how sensitive we are to the alluring cue or context in the environment. This work has been funded by a collaborative NSF grant (PI: Shoda).

Dr. Casey with Drs. Mischel and Kevin Ochsner (PI) of Columbia University are working on another addiction related project. 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 recently funded by NICHD (PI: Ochsner).

Translational Mouse and Human Studies

The Sackler Institute has established a high profile in genomic research translating transgenic mouse models to human behavior and disease. 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).

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. The 5-HTT KO mouse shows impaired 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 and have been submitted for publication.

Development of Extinction. Siobhan Pattwell, a neuroscience student in Dr. Francis Lee's lab, and Dr. Stephanie Duhoux, a post doctoral fellow with Dr. Casey, are examining the development of extinction related behavior in pre-, peri- and post adolescent mice and humans. The preliminary evidence suggests that adolescents show less extinction than preadolescents or adults. These findings have significant implications for when exposure therapy may be most beneficial given that this treatment relies on principles of extinction. A NIH TR01 has been submitted by Drs. Casey, Lee and Glatt to follow-up these findings.

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. Our studies are focused on determining the efficacy of innovative therapies and preventive strategies for disorders as a function of developmental status and potential genetic effects inferred from mice and humans.

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 funded by an NIMH K99/R00.

Genetic and Imaging Studies of Eating Disorders. Dr. Casey and MD PhD candidate, Megan Riddle, are collaborating on several 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). A third study in collaboration with Dr. Glatt examines the anxiolytic effects of diet restriction in mice and humans with anorexia nervosa on expression of the serotonin transporter gene (rs3813034).

Education and Training

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, UCLA, Vanderbilt, 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 activities are provided below.

2010 Summer Institute. Dr. Casey received funding for a tenth annual summer institute on the biology of developmental disabilities from the John Merck Fund. This past year's course was co-directed by Drs. Casey 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. Beginning in 2012 this summer institute will be renamed as the Mortimer D. Sackler, M.D. Summer Institute and supported by a generous gift by the Mortimer D. Sackler, M.D. Sackler family.

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 70 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. Zevin, 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. 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 have resulted in participation of the medical students in rotations and Sackler seminars.

Neuron to Brain. Drs. 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.

Biology of Neural Disease Course: Molecule to Bedside. Drs. Casey, Betsy Ross and Giovanni Manfredi are co-directing a course on biology of neural diseases focusing on three categories of disorders: neuropsychiatric (anxiety), neurodevelopmental (autism), and neurodegenerative (Parkinson's disease). The course is geared for PhD students to provide exposure to specific patient populations.

Fundamentals of Cognitive Neuropsychology. Dr. Jason Zevin teaches an honors seminar at Barnard College as an adjunct faculty member. A number of students from this course have gone on to pursue graduate studies in related areas, including Gina Marrone, a current doctoral candidate in the Neuroscience Program.

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 4 years and has received an NICHD T32 joint institutional interdisciplinary training grant submission for predoctoral fellows in development and learning (see <http://neuroscience.cornell.edu/imagine.html>).

Recruitment of Underrepresented minorities. Dr. Casey participates in the Gateway and Access programs that provide summer mentorship for underrepresented minorities who may be potential MD, PhD and PhD applicants to Weill Cornell.

Outreach Activities

This year has been a significant one for outreach related activities in local, national and international settings. We provide a few examples of these efforts below.

The Garage, Moscow Russia. In collaboration with renowned interactive artist, Marina Abramovich, Dr. Jason Zevin together with Drs. Casey, Dan Stern, Nadia Brushweiler and Myrna Weissman as well as Ilene Sackler Lefcourt, Bob Wilson, and Jorn Weisbrodt, are putting together both a scientific and public exhibit on neural correlates of personal interaction based on electrophysiological recording during extended periods of eye contact building upon Abramovich's exhibit "The Artist is Present" at the MoMA.

American Museum of Natural History. Drs. Casey and Somerville both gave lectures on the brain as part of museum offered courses.

Neuroscience and the Law. Dr. Casey was invited to speak at the Sackler Forum on Neuroscience and the Law, jointly sponsored by the Royal Society and NAS on adolescent brain development. She has also been invited to speak at the annual NAS meeting in May. In addition, Dr. Casey is currently involved in a report sponsored by the IOM on Juvenile Justice Reform.

Board on Children Youth and Families. Dr. Casey sits on the Board of Children, Youth and Families as an expert in developmental neuroscience. She has been centrally involved in a report on the "The Science of Adolescent Risk Taking" and more recently is focusing on cognitive impairment in children following cancer treatment and on concussions in school athletes.

Office of Adolescent Health. Dr. Casey was a keynote speaker at an OAH meeting on teen pregnancy intervention, during which she presented the science of risk taking behavior in teens.

Media Publicity. Dr. Casey has been interviewed by PBS, Time Magazine, Charlotte Observer, National Geographic, BBC radio, APA Psychiatric News, *Today's Science*. Facts On File News Services in addition to her work being covered in University publications and websites.

Special Issue of Biological Psychiatry. Dr. Amy Arnsten of Yale and Dr. Casey recently collaborated on a special issue of Biological Psychiatry to emphasize a role of systems neuroscience in psychiatric research and medicine that will come out this year.

Grants and Awards

Grants and Awards (2010-2011)

Dr. Casey was awarded a subcontract on a NIDA R01 with Drs. Ochsner and Mischel of Columbia University 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. 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. Charles Glatt received a NIMH R21 to investigate the functional effects a new serotonin transporter polymorphism.

Dr. Somerville was awarded a K99/R01 grant to examine transient and sustained emotional regulation processes across development.

Dr. Zevin was awarded a subcontract to study the role of episodic memory and consolidation in predicting success in literacy acquisition, in collaboration with Kenneth Pugh and colleagues at Haskins Laboratories. The proposed work will examine a previously under-studied relationship between individual differences in basic memory processes and literacy skill.

Dr. Zevin was awarded a subcontract to study cross-language literacy acquisition in an international study coordinated among Weill Cornell, Haskins Laboratories and Hebrew University of Jerusalem. The study will assess the extent to which acquiring literacy in a second language necessarily entails developing native-like processing abilities in details that differ sharply between writing systems.

Pending Grants and Awards

Drs. Casey, Glatt and Lee submitted a NIH Transformative R01 application to examine neurodevelopmentally guided preventive and personalized medicine. A fundamental issue in psychiatric medicine is the lack of empirical evidence for when, during development, an intervention or treatment will be most (or least) effective for preventing or treating mental illness. This application uses a developmentally guided translational approach to delineate windows of maximal change in behavior by focusing on basic forms of emotional learning and memory that are at the very core of behavioral therapeutics. The objective is to determine the efficacy of innovative therapies and preventive strategies for psychiatric disorders as a function of developmental status and to determine potential genetic effects inferred from mice and humans.

Dr. Casey is collaborating with Larry Steinberg of Temple, Adriana Galvan of UCLA and Buffie Scott of Columbia on a MacArthur Neuroscience and the Law Network initiated project related to juvenile justice policy. They plan to examine behavioral and brain development specifically relevant to socioemotional contexts most common to criminal behavior in cohorts of youth in the LA and NY area.

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. Zevin has submitted an NICHD R01 to study second language learners' use of information at multiple levels of description in order to compensate with difficulties in speech sound categorization documented in his current work.

Dr. Zevin, in collaboration with Dr. Lori Holt (co-PI, CMU), Fred Dick (co-PI, Birkbeck) and Natasha Kirkham (co-PI, UCL) has submitted an NICHD R01 to study statistical learning with emergent functional. The proposal incorporates studies of infant development and functional

neuroimaging to examine links between perceptual category learning and the tracking of transitional probabilities in sequences of simple auditory and visual stimuli.

Dr. Zevin was included as Co-Director of a computational modeling core in a P01 application submitted to NICHD by Robin Morris (co-PI, GA Tech), Maureen Lovett (co-PI, Hospital for Sick Children) and Kenneth Pugh (co-PI, Haskins Labs). The project will use a well-respected intervention program for reading disability to identify "non-responders" and examine their profiles on a set of general measures of language and memory processing abilities.

Dr. Zevin, collaborating with Bruno Tagliaferri (co-PI, Perception Research Systems), 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, collaborating with Bruno Tagliaferri (co-PI, Perception Research Systems), is preparing to submit an NIMH R43 application to develop software that will enable researchers to easily design experiments and collect data using tablet devices (such as the iPad, which has obvious advantages for developmental research).

Dr Zevin is preparing an NICHD R01 in collaboration with Hua Shu (Beijing Normal University) and Jianfeng Yang (Chinese Academy of Sciences) to continue their collaborative work combining computational modeling and functional neuroimaging to examine similarities and differences in the reading circuit between English and Chinese.

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.

Publications

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