

The Sackler Institute for Developmental Psychobiology
Weill Cornell Medical College
Annual Report for June 2007-May 2008

The Institute has established a high profile in genomic and translational neurodevelopmental research under the direction of Dr. BJ Casey as evidenced by a recent NIMH Center grant in this area being awarded to The Institute. Faculty and fellows have received a number of awards this year (See *Grants and Awards*) and training remains a priority with the continuation of the annual Summer Institute on the *Biology of Developmental Disabilities* and increased involvement in medical and graduate student training and elementary and high school (see *Education, Training and Outreach*). We have published 65 manuscripts this past year and highlight a few of these studies in this report (see *Program of Research and Publications*).

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

Bruce D. McCandliss, Ph.D., Associate Professor of Psychology in Psychiatry

Michael Posner, Ph.D., Professor of Psychology in Psychiatry, Emeritus

James Swanson, Ph.D., Part-time Professor of Psychology in Psychiatry

Nim Tottenham, Ph.D., Assistant Professor of Psychology in Psychiatry

Jason Zevin, Ph.D., Assistant Professor of Psychology in Psychiatry

Sackler Staff

Deanne Lamb, Institute Administrator

Emmanuel Stein, IT Manager

Sackler Research Assistants

Juliet Davidow, Research Assistant

Jamie Ferri, Research Assistant

Sarah Getz, Research Assistant

Tara Gilhooly, Research Assistant

Rachel Koister, Research Assistant

Alexander Millner, Research Assistant

Cathy Yun, Research Assistant

Sackler Predoctoral and Postdoctoral Fellows

Thomas Farmer, Cornell-Weill Sackler psychology Ph.D. student

Yang Jianfeng, Ph.D., Postdoctoral fellow

Rebecca Jones, Neuroscience Ph.D. student

Liat Levita, Ph.D., Sackler Instructor

Conor Liston, MD, Ph.D., Weill Cornell Psychiatry Resident

Martijne Mulder, Medical University of Utrecht, PhD student

Jeremy Skipper, Ph.D., Postdoctoral fellow

Fatima Soliman, Tri-Institutional M.D., Ph.D. student

Yuliya Yoncheva, Neuroscience Ph.D. student

Kevin Bath, Ph.D., Lasdon-Sackler Postdoctoral fellow

International Sackler Scholars

Oana Benga, Babes-Bolyai University, Romania

Sarah Durston, University of Utrecht, The Netherlands

Annette Karmiloff-Smith, University College London, United Kingdom

Urs Maurer, Swiss National Science Foundation, Switzerland

Gaia Scerif, University of Oxford, United Kingdom

Program of Research

This year, several empirical studies have been completed and published using the techniques of brain imaging, human 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 of these studies representing three general domains of study: 1) learning and development, 2) imaging and behavioral genetics; and 3) neurobiology and risk factors for developmental disorders.

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 several of these studies below across the domains of perceptual, emotional and cognitive learning.

Neural Basis of Statistical (Unsupervised) Learning. Dr. Dima Amso is examining the neural basis of unsupervised learning in habituation and novelty preference studies. She is currently examining these abilities in infants and children using eye tracking and magnetic resonance imaging methods. This work lays the groundwork for identification of learning disabilities early in life and forms the basis of Dr. Amso's recent NIMH K-award and a recently awarded NIMH Center grant to The Institute.

Attention and Perceptual Learning in Infancy. 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 studies, Dr. Amso is investigating the mechanisms of the development of visual selection and how they play a role in efficient attenuation of distractor information during learning. Her work suggests that where infants look determines what they perceive and is dependent on their ability to control their eye movements.

Object Learning in Infancy. Infants as young as 4 months fail to show surprise when occluded moving objects fail to emerge from behind a static object, indicating that they do not form a visual memory of the object and its trajectory while it was occluded. By 6 months, infants indicate understanding of this continuity and can use this information to guide crawling and reaching. When infants are exposed to the relevant information about an object's trajectory they can perform this task at an earlier age. Dr. Amso is using electrophysiological measures to constrain current developmental theory on how infants can use repetition to learn to organize their environment.

Object Learning in Children. Faces are a special class of objects as humans have vast experiences with them over the life span. Dr. Nim Tottenham has found that children process faces faster than inanimate objects therefore suggesting that extensive exposure with one class of objects can affect the speed of processing and explain developmental differences consistently found in the literature on face processing. Parallel imaging studies show that brain activity in the fusiform face area is enhanced in response to faces over other objects and

increases with age. Developmental disorders such as autism, in which faces appear to be processed differently, may be better understood using information gained from this study. Preliminary findings from this work are published in *Developmental Science*.

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. Amso and Tottenham together with Sacker fellows Megan Fitzgerald, Juliet Davidow, and Tara Gilhooly, are examining how individual differences in information gathering, via shifts of eye gaze, support the ability to discriminate between emotional expressions in infants. This work provides a developmental framework for examining face processing deficits in autism.

Development of Emotion Regulation. Drs. Casey, Hare and Tottenham together with Rebecca Jones, Sarah Getz and Alex Millner are examining the interaction of limbic and prefrontal circuitry in regulation of emotions in children. This work is supported by a NIDA R01 to Casey and was the basis of a NRSA and doctoral dissertation by Todd Hare, now a post doctoral fellow at Cal Tech. Hare has shown that adolescents have an initial heightened response to emotional information in limbic brain regions relative to children and adults. This project forms the foundation for parallel studies of children with problems in emotional and behavioral regulation (e.g., PTSD, anxiety, depression and, previously institutionalized), a NIMH Center grant to The Institute and recent Hartwell award to Sackler affiliated faculty member, Dr. Charles Glatt. This work will be highlighted by PBS in a special documentary on adolescent depression in May 2008 and published in *Biological Psychiatry* that same month.

Fear Conditioning and Extinction. A core problem in many children 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 and Dr. Liat Levita an instructor at The Institute, under the mentorship of Casey and Lee, have developed paradigms for examining this type of learning with fMRI and galvanic skin responses. Parallel studies are being performed in the rodent in collaborative studies with Drs. Lee and Bath and two PhD students Siobhan Patwell and Rebecca Jones.

Development of Speech Perception in Children and Adults: Drs. Bruce McCandliss and Jason Zevin are 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. They examined the effects of Childhood vs. Adulthood experience with a language and show that it impacts perceptual responses to speech, as revealed by eye movements while reaching for objects. This work is supported by an NIDCD R01 to Drs. McCandliss (PI) and Zevin, for which McCandliss recently received the Presidential Early Career Award for Scientists and Engineers.

Habituation Studies of Speech Perception. Bruce McCandliss is testing whether greater responses to novel stimuli following a train of standard sounds reflects habituation followed by dishabituation or a top-down effect that might be better characterized as change detection or orienting to change. Preliminary results favor the later explanation and suggest a reevaluation of neural mechanisms underlying these processes.

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 Drs. McCandliss and 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 serves the basis of a recently submitted NIH K99 grant application (PI: Skipper).

Reading in multiple languages. Yang Jianfeng is a postdoctoral fellow working with Drs. Zevin and McCandliss on computational modeling of the development of reading in multiple languages. The focus of this work is to study the differential contribution of basic perceptual and cognitive processes to reading in different writing systems, which will help explain why reading disorders present in culturally-specific ways, despite significant overlap in the neural substrate for reading across languages.

Genomic Investigations

The Sackler Institute is rapidly establishing a high profile in genomic research that represents an elegant mapping of human and animal projects that examine gene-environment interactions in developing humans and transgenic mouse models.

Gene-Environment Interactions across Development: In a unique marshaling of the talents of scientists with expertise in pediatric imaging, molecular biology, mouse models, and neurotrophins, BJ Casey (PI), Francis Lee, Dima Amso, Nim Tottenham, Charles Glatt, Kevin Bath and Andy Leon of the Department of Psychiatry, Barbara Hempstead of the Department of Medicine and Henning Voss of the Department of Radiology and Andrew Clark, Carlos Bustamante and Jason Mezey at Cornell University have received a NIMH P50 Interdisciplinary Developmental Research Center application to examine the impact of brain-derived neurotrophic factor (BDNF) and experiential events (e.g., stress, trauma, enrichment) on learning and development, and on vulnerability and resistance to psychopathology. This work builds on pilot data supported by the generous gift of the Mortimer D. Sackler family and based on collaborations among faculty and fellows of Lasdon Laboratories and the Sackler Institute within the Department of Psychiatry and forms the foundation for parallel studies of children with problems in emotional and behavioral regulation (e.g., PTSD, anxiety, depression and, previously institutionalized),

Genetic Influences on Emotional Regulation in Adolescents. Taking a vertical integration approach, Charles Glatt (PI) in collaboration with BJ Casey will be examining the molecular, neural and behavioral phenotype of a newly discovered polymorphism in the serotonin transporter gene across development, specifically focusing on adolescence when there is an increase in incidence of depression related suicide and prevalence of affective disorders. This work is supported by a Hartwell grant.

Individual differences in Fear Conditioning and Extinction. Fatima Soliman under the mentorship of Drs. Casey and Lee, have developed paradigms for examining conditioning and extinction with fMRI and using galvanic skin responses and genetics to constrain interpretations about risk genes and individual differences. Parallel studies are being performed in the rodent in collaborative studies with Drs. Lee and Kevin Bath and two PhD students Siobhan Patwell and Rebecca Jones.

Biological Differences Underlying Sensitive Periods in Language Learning. This McDonnell grant (PI: Maurer) subcontract to McCandliss parallels an ongoing NIH-R01 (PI: McCandliss) investigation of the sensitive period effects in speech perception. This work provides a collaborative effort of 6 labs around the world looking at different aspects of critical period effects from different perspectives. The Sackler Institute will contribute a unique set of studies examining how learning language changes from age 6 to 18, and link these changes to genetic polymorphisms, white matter tract measures of developmental changes in myelination, and Tanner stages of pubertal development.

Clinical Investigations: Risk Factors and Interventions

The overarching mission of the Sackler Institute is to delineate the biological mechanisms underlying developmental disabilities to direct treatments and interventions and hopefully ameliorate these disorders in the future. The majority of studies currently underway focus on risk factors for mental illness and treatments and interventions for the disorders of dyslexia and autism. Other areas of research in this area include examination of the long-term effects of psychological stressors (e.g., institutionalization and stress following treatment for breast cancer). These latter studies are moving the field toward individualized treatment and intervention approaches to stress related diseases, based on identified genetic and environmental risk factors discussed in editorials and reviews in the *American Journal of Psychiatry* and *Current Opinions in Neurology*.

Studies of Autism: A number of recent studies of autism have suggested a deficit in eye gaze may underlie problems in processing social information from faces. Dr. Nim Tottenham, in collaboration with Dr. Margaret Hertzog and Tara Gilhooly, is investigating the development of face processing in autism by examining the neural consequences of atypical visual scanning of faces in autism. Dr. Tottenham has received a grant from National Alliance for Autism Research-Autism Speaks foundation to help support this research. Findings from these studies are currently being used to develop a laboratory-based intervention for poor face processing in autism.

Biomarkers for autism – One of the imperatives in the field of autism is early diagnosis. In collaboration with Drs. Barbara Hempstead & Francis Lee, Dr. Nim Tottenham is investigating a potential biomarker (peripheral BDNF) for autism. Using a translational approach, the behavioral consequences of this biomarker will be examined in a mouse model and as well as individuals with autism across development.

Studies of dyslexia. This NIH R01 (PI: Kasner) subcontract to McCandliss uses high resolution fMRI scanning to isolate functional activity in magno- versus parvo-cellular pathways in the thalamus of typically reading and dyslexic adults. This study provides the most direct test to date of the 'magno-cellular deficit' hypothesis as a critical neurobiological cause of dyslexia.

Brain Development 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. The effects of prior institutionalization on the structural and functional development of limbic circuitry using magnetic resonance imaging (MRI), are being explored by Drs. Casey and Tottenham. They are examining the association of hippocampal and amygdala volume with length of institutionalization, age at institutionalization, and length of time with an adopted family. The preliminary findings are consistent with the animal and human imaging work on chronic stress leading to structural and functional changes in the hippocampus and amygdala that are inversely related. Current investigations focus on the functional significance of these anatomical changes and on the genetic contributions to these phenotypes following stress. These preliminary data have resulted in a NIMH funded R01 grant to Dr. Casey and served, in part, as preliminary data for a NIMH Center grant, which we have been awarded.

Effects of Psychological Stress on Prefrontal Cortex: Dr. Casey and Conor Liston, a soon to be graduate of tri-institutional M.D., Ph.D. program and resident at Weill at Weill Cornell as well as recipient of the Soros and Perry Awards, have examined in humans and animals the impact of moderate stress in collaboration with Dr. Bruce McEwen of The Rockefeller University. Both species show changes in attention shifts, but not behavioral set shifting, following stress that normalizes once the stressor is removed. Human imaging and animal histological studies show changes in prefrontal cortical regions that support attention shifting. Imaging and animal data from this study have recently been published in *Neuron*, *J*

Neuroscience and under review at *Nature*. This work formed the basis for a DOD grant submission by Dr. Mary Charlson (PI), Chief of General Internal Medicine, Liston and Casey to elucidate the biological and neural mechanisms through which meditation acts to ameliorate the psychological and functional consequences of stress and radiation among patients with radiation-treated cancer.

Risk-taking in Teens. Casey together with Drs. Elke Weber and Bernd Figner of Columbia University, are examining the development of risky behavior in adolescents using both fMRI and gambling card task. Preliminary behavioral data show teens to be more risky than children or adults. These results are consistent with earlier work at The Institute showing elevated activity in brain regions involved in risky choices in teens relative to children and adults and the work is supported by a recent NSF grant (PI: Weber) and forms the basis for a developmental framework for examining risk for substance abuse in teens

Individual and Developmental Differences in the Delay of Gratification: 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. This work is essential as toddler measures of delay of gratification have been shown to be related to substance abuse in adulthood. Preliminary results suggest those individuals most able to wait for a reward, as a toddler, were 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, and University of Michigan has been awarded to support this program of research. Preliminary findings are published in *Psychological Science*.

Learning-based changes in academic skills in children: Dr. McCandliss has been funded by the McDonnell Foundation to explore novel learning paradigms that engage adults in learning a new alphabetic writing system with novel fMRI activation tasks to measure the impact of learning. A follow-up National Science Foundation funded project, in collaboration with Stanford, uses learning-based changes in fMRI responses by children to contrast different computer-based intervention programs designed for basic reading and numerical skills. This work is leading to a set of novel educational interventions for number processing skills now being carried out in schools in California for assessment of potential positive impact on mathematics skills. A subsequent NSF grant has been submitted by McCandliss to further examine the effects of age and instruction on math abilities that has received very favorable review.

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, Oxford, London, Switzerland and The Netherlands in addition national ones with Berkeley, Brookhaven Laboratories, Brown University, Cornell-Ithaca, Columbia, Duke, Mt. Sinai, NIMH, NYU, University of Oregon, Pennsylvania, Princeton, Rockefeller, Stanford, UC-Irvine, University of Pittsburgh and Yale and with research fellows from Finland, Switzerland, and The Netherlands. Highlights of the Institute's training and outreach program are provided below.

Summer Institute on the Biology of Developmental Disabilities. Casey has received funding for a seventh 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 Drs. Jason Zevin and BJ Casey of the Sackler Institute and Barbara Finlay of Cornell University and will focus on training psychologists and neurobiologists in methods used in developmental neuroscience (imaging, genetics, and behavior) in the context of the central themes of learning and development (see: <http://www.sacklerinstitute.org/cornell/summerinstitute/>).

The Sackler Summer Science Experience. Bruce McCandliss's team has developed a Summer

Science Experience for elementary children with an interest in science. The children are invited to a five session ‘summer brain camp’ in which they participate in and learn about all the research protocols while also engaging in interactive learning experiences focused on brain anatomy and function, developed in collaboration with a teacher from the New York City Public School system. This program has proven to be popular with children, and included their participation in eye tracking, EEG, and fMRI studies.

Developing Researchers in Neuropsychiatric Imaging. The Institute actively participates in summer workshops with the Functional Neuroimaging Laboratory directed by Drs. David Silbersweig (PI) and Emily Stern as part of a NIMH R25 Grant to train researchers in neuropsychiatric imaging.

Weill Graduate School of Medical Science. Dr. Casey is the incoming 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 MD PhD program.

Brain to Mind. Drs. Amso, Casey, Tottenham and Zevin all played significant roles this year in teaching medical students at Weill Cornell and Weill Quatar 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, McCandliss, Tottenham and Zevin all played significant roles this year in teaching Weill Biomedical Graduate Program in Neuroscience related courses that link brain and behavior across learning. Some of the best teaching evaluations were given to this group, with highest praise to Drs. Amso and Tottenham, for their lectures on attention and affective neuroscience.

Ithaca-Weill Joint Graduate Program in Development and Learning. Dr. Casey in collaboration with Dr. Barbara Finlay of Cornell University-Ithaca have hosted joint campus meetings of psychology and neuroscience faculty for the past two years and have submitted a NIH T32 joint institutional interdisciplinary training grant submission for predoctoral fellows in development and learning (see <http://neuroscience.cornell.edu/imagine.html>). The grant received a 151 priority score and is being resubmitted.

UK-NY Sackler Institutes Meeting. An international meeting of the Sackler Institutes in the US and UK was hosted by Eve Johnstone, the Director of the Sackler Institute at the University of Edinburgh and the faculty. Presentations by Drs. Casey, Glatt, Lee, Levita and McCandliss were given as part of efforts to increase collaborations across Institutes in genetic and imaging research.

Columbia-Cornell Sackler Institutes Meeting. The annual joint meeting of the NY based Sackler Institutes will be hosted by Myron Hofer, the Director of the Sackler Institute at Columbia and Sackler faculty and fellows this April. These meetings have resulted in joint mentorship of fellows and collaborative research studies.

Grants and Awards

Grants and Awards (2007-2008)

Dr. Dima Amso received a five-year NIMH K01 award to examine statistical learning in infants and children using electrophysiological and magnetic resonance imaging methods under the mentorship of Dr. Casey. This work will form the basis for later studies on identification of learning disabilities early in life.

Dr. Casey received a \$10 million center grant from the NIMH to examine gene X environment interactions across development. This center is a joint Weill-Ithaca campus initiative involving

Francis Lee, Dima Amso, Nim Tottenham, Charles Glatt, Kevin Bath and Andy Leon of the Department of Psychiatry, Barbara Hempstead of the Department of Medicine and Henning Voss of the Department of Radiology and Andrew Clark, Carlos Bustamante and Jason Mezey at Cornell University.

Dr. Casey in collaboration with Elke Weber (PI) and Bernd Figner of Columbia University and Mauricio Delgado of Rutgers received a collaborative NSF grant to examine the development of risky decisions during adolescence using fMRI.

Dr. Casey received a grant from the John Merck Fund to support the 8th annual Summer Institute on the Biology of Developmental Disabilities that she has been directing for eight years.

Dr. Casey was awarded the Outstanding Graduate Alumna of the College of Arts and Sciences by the USC, where she completed her graduate work.

Dr. Charles Glatt (PI), a Sackler affiliated faculty member, in collaboration with Casey received a Hartwell grant entitled A Mechanistic Study of Genetic Influences on Emotional Regulation of Behavior to examine the molecular, neural and behavioral phenotypes of a newly identified polymorphism in the serotonin transporter.

Dr. McCandliss received the Presidential Early Career Award for Scientists and Engineers from the National Institute on Deafness and Other Communication Disorders (NIDCD). The award recognizes Dr. McCandliss' research on the biological basis for language development and dysfunction in developmental disorders such as dyslexia. Nationwide, only a total of 56 such awards were granted.

Pending Grants and Awards

Drs. Casey and Conor Liston, in collaboration with Dr. Mary Charlson (PI), Chief of General Internal Medicine, submitted a DOD grant to elucidate the biological and neural mechanisms through which meditation acts to ameliorate the psychological and functional consequences of radiation treatment and stress and improve quality of life among cancer patients.

Dr. Casey in collaboration with Dr. Barbara Finlay of Cornell University-Ithaca have submitted an NIH T32 cross campus interdisciplinary training grant for predoctoral fellows in development and learning. This application 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. McCandliss has a Phase II STTR application pending on his continued work to interface research modalities used in developmental cognitive neuroscience

Dr. McCandliss has a NSF grant application pending on brain correlates of early math and number skills tracing changes related to age and instruction in a natural experiment that has received a highly favorable review.

Dr. Jeremy Skipper has submitted a K99 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. Nim Tottenham together with Drs. Barbara Hempstead & Francis Lee, have submitted an application to the Simon Foundation to investigate a potential biomarker (peripheral BDNF) for autism.

Dr. Zevin has submitted an R21 application 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.

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

Publications

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- Dennis, T., Chen, C.C., & McCandliss, B.D. (in press). Threat-related attentional biases: an analysis of three attention systems. *Anxiety and Depression*.
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