

## **Annual Report of the Sackler Institute/Weill Medical College of Cornell University**

July 01, 2002-June 30, 2003

During the past year, the Institute has been under the direction of Dr. BJ Casey with Dr. Posner's retirement last year to his home in Eugene. The Institute's international reputation in research and training in the field of human brain development is at its highest ever with increasing numbers of faculty and fellows spending sabbaticals, internships, and summers at the Institute (see Education, Training and Outreach). The Institute's networking mission has been broadened with collaborations now formally established with Princeton, Yale, Columbia, Duke, UC-Berkeley, Stanford, Brookhaven, Mt. Sinai, U. Penn, UC-Irvine, NIMH, and Oregon and with pre and postdoctoral fellows from Spain, Norway, U-Penn, Minnesota, the Netherlands, and the College London. A significant number of empirical studies have been completed and published using the methods of brain imaging, genetics, high density EEG, eye movements and behavioral training, to study populations from childhood to adulthood. Below, research studies on perception, attention, and cognitive control in typically and atypically developing populations are described. Clinical/intervention and genetic research initiatives are highlighted in separate sections. A significant objective of the Sackler Institute is in education, training and outreach. Efforts in this area are highlighted followed by a list of grants, awards and nearly 60 publications providing supporting documentation for this report.

### **Research**

#### 1) Studies of Perception and Attention

##### Ongoing Projects:

Dr. Bruce McCandliss and Fulbright Scholar, Maria Ruz from Spain, are investigating the extent to which word reading is automatic. Their electrophysiological results suggest that word processing, is an automated process that takes place even when attention is engaged in a simultaneous demanding task. In collaboration with Dr. Mariano Sigman of Rockefeller University, now at INSERM in Paris, Dr. Michael Worden has been investigating how subcomponents of this ability develop. He is examining the neural processes underlying perceptual learning in the visual system. His data support the hypothesis that extensive practice induces changes in processing in low-level visual brain areas and are mediated by feedback connections rather than by modifications of intrinsic circuitry in those low-level areas. Ongoing work in this area is attempting to further characterize the changes that occur in the visual system as a result of practice and to understand how these changes relate to visual attention, brain plasticity and reading.

##### New Projects:

Dr. BJ Casey and PhD candidate, Nim Tottenham, have been developing behavioral assays for measuring subconscious perceptual processing of faces in children. Given the vast experience with faces, the finding that children process faces faster than other objects (houses) suggests that extensive experience with one class of objects can affect the speed of processing of these objects over others and explain developmental differences consistently found in the literature on face processing. Parallel imaging studies show that activity of the fusiform face area can be modulated by attention to or away from a face stimulus. Tottenham and Casey used functional magnetic resonance imaging to demonstrate modulation of the fusiform face area to faces as a function of stimulus presentation time relative to processing the less familiar category of houses.

Faces presented subliminally with a mask-elicited activity in the fusiform face area, but this activity increased as the faces were processed more consciously. This pattern of activity was not observed for those brain areas (e.g., medial fusiform gyrus) that have been shown to be activated by house stimuli or less familiar categories of objects. This work supports the notion that the fusiform face area has adapted to support processing of familiar objects with which we have extended expertise such that they may be processed without the need of attentional control. This groundbreaking developmental research is important for understanding developmental disorders that appear to process faces differently (e.g. autism).

## 2) Studies of Cognitive Control

### On-going Projects:

The Sackler Institute has been working on tasks that would allow us to understand the development of control systems from childhood to adulthood. Some of our discoveries and the related papers are discussed below.

An important component of control processes is overriding inappropriate thoughts and actions. This year the Institute published findings showing a delay in the development of frontostriatal circuitry underlying this ability in 6 to 11 year olds in two different studies (Casey et al 2002, Durston et al., 2003). These tasks are now being used with developmental disorders that have as a core problem, difficulty overriding inappropriate actions (ADHD and OCD) as part of two separately funded Institute projects from the NIMH (See Clinical/Intervention studies). A third study by Dr. Casey examined the role of this circuitry in attention-switching as this ability also requires that the subjects control where and to what they attend. The results show robust bilateral activity of the caudate nucleus across age groups during the task switching condition with only adults showing significant activity in superior frontal and parietal regions. The results suggest an important role of the caudate nucleus in simple task switching across development with increasing recruitment of cortical regions with maturity.

### New Projects:

Under a recent R21 NIDA grant by Dr. Casey in consultation with Dr. Nora Volkow of Brookhaven National Laboratories, the institute has begun studies on the development of prediction and reward related circuitry relevant for understanding substance abuse and prenatal exposure to substances on brain development. Dr. Matt Davidson, a postdoctoral fellow with Dr. Casey has taken the lead on these studies in collaboration with Dr. Jon Hortvitz of Columbia and Dr. John Fossella, of the Sackler Institute.

This past year has been one of success in combining and using new brain imaging methodologies to examine attention and control related circuitry. Conor Liston, a tri-institutional MD, PhD student and Dr. Casey used a relatively new technique of diffusion tensor imaging to assess directionality and myelination of axonal tracts in vivo in the developing human brain. Preliminary results from callosal and frontostriatal fiber tracks show greater diffusion in children compared to the adults ( $p < .05$ ) consistent with developmental changes in frontal and callosal white matter with age. This technique may prove useful in delineating developmental delays in clinical disorders. Drs. Jin Fan and Mike Worden have been using a combination of high-density EEG and fMRI to explore the interaction that occurs between different prefrontal, frontal-midline and other brain areas associated with subjects monitoring their own behavior and mistakes. Such work may prove significant when investigating disorders such as conduct disorder.

### 3) Genomic Investigations

#### Ongoing Projects:

Dr. Jim Swanson has continued molecular genetic investigations of ADHD using laboratory tests to measure quantitative traits for use in candidate gene studies of the dopamine 4 receptor and dopamine transporter genes. He has developed a collaboration with the National Human Genome Research Institute (NHGRI) to perform a genome scan of ADHD children and controls and has received a NIH R01 to investigate genetics of ADHD.

Drs. Fan and Fossella have continued their genetic and imaging work on attentional control. They suggest the involvement of genetic variants in monoamine oxidase A (MAOA) and dopamine receptor gene (DRD4) in attentional control and patterns of brain activity in the anterior cingulate cortex, a region implicated in attentional control (see Fan et al. 2003, PNAS). These results are important in the context of ADHD and schizophrenia research where the anterior cingulate cortex and catecholamines have been postulated to play a significant role.

#### New Projects:

Drs. John Fossella and Casey have been examining the association between patterns of prefrontal brain activity and variants in catecholaminergic genes. In recent findings in collaboration with Sonia Bishop at U Penn, they show that the magnitude of the dorsolateral prefrontal cortical response evoked by emotional distractors differs between individuals with the 3- versus 4- repeat copy allele of the MAOA-LPR polymorphism. The MAOA gene plays a role in catalyzing the degradation of catecholamines. The 3 and 4- repeat copy MAOA-LPR alleles are most common, with the 4-repeat allele having 5- fold higher levels of expression and hence being associated with reduced catecholamine levels. Individuals with the 'low expression/high dopamine' 3-repeat allele showed reduced DLPFC activation when performing a matching task in the presence of emotional (versus neutral) distractors relative to individuals with the 4-repeat allele. This result is consistent with the suggestion that heightened catecholamine levels mediate a reduction in PFC activity in the presence of emotional stimuli.

### 4) Clinical Studies

The Institute continues work to translate its methods for use with clinical populations. Currently our experimental assays for analyzing attentional deficits are in use by a wide range of researchers working in diverse areas such as schizophrenia, depression, anxiety, ADHD, OCD, autism, abuse and genetic deletion syndromes. We have continued to work with the residents in Psychiatry in joint clinical reading and research projects. In addition recent experimental results of particular relevance to clinical issues are briefly discussed below.

#### On-going Projects:

Dr. Casey is examining the effects of prior institutionalization on the structural and functional development of the amygdala and hippocampus using magnetic resonance imaging (MRI). She and Nim Tottenham have examined the association between hippocampal and amygdala volume with length of institutionalization, age of institutionalization, and length of time with an adopted family, controlling for overall cerebral volume and current age. The preliminary findings are provocative, suggesting an inverse relation between volumetric measures of the amygdala and hippocampus for institutionalized children but not typically developing children. Further, they show a dissociation between hippocampal and amygdala volume in their relation to months in

institution ( $r = -.76$  and  $r = .77$ , respectively) and months with adopted family ( $r = .64$  and  $r = -.76$ , respectively), after controlling for age and cerebral volume. These 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. The association between these structures and time with adopted family suggests resilience and plasticity in these regions. This preliminary data has resulted in a R01 submission by Dr. Casey in collaboration with Dr. Mary Altemus of Lasdon Labs and consultation with Dr. Bruce McEwen of The Rockefeller University.

Dr. Swanson has made progress in diagnosis, and pharmacological treatment of ADHD. His work in this area focuses on understanding the mechanisms of action of stimulant medications. The studies include: a comparative study of different preparations of methylphenidate that have been recently approved by the FDA for once-a-day administration to ADHD children; a continuation of the MTA study of the long-term effects of pharmacological and psychosocial interventions; and a continuation of the Preschool ADHD Treatment Study (PATs) that involves pre-treatment with behavioral interventions followed by treatment with methylphenidate (Swanson et al 2002).

In a related study, Dr. Casey in collaboration with Duke, Columbia, Stanford and UC Berkeley, is examining the imaging profiles of children and their parents with ADHD on behavioral assays she has developed at the Institute. Preliminary findings on this clinical population are published in Biological Psychiatry (see Durston et al 2003) and show abnormal patterns of brain activity in the caudate nucleus rather prefrontal regions.

Dr. McCandliss continues his behavioral and fMRI investigations of reading skills. During this latest period he has launched initial data collection efforts involving first grade children with a test battery approved by the New York City Board of Education. He and his staff are currently collecting behavioral reading data from 150 first grade children whose parents have opted into the study following recruitment in 18 New York City public elementary schools. During the summer a subset of these children that demonstrate deficits in reading skills will be invited to participate in fMRI scans of brain activity related to reading.

#### New Projects:

Dr. McCandliss has received a subcontract from the Brain Trauma Foundation as part of a 3 year multimillion dollar grant from the J. S. McDonnell Foundation on "Cognitive and Neurobiological Research Consortium in Traumatic Brain Injury." This project will work on identifying three separate brain networks associated with sub-components of attention (Fan, McCandliss, Somer, Raz, and Posner, 2002) to understand deficits in mild traumatic brain injury. The central hypothesis is that deficits in mild brain injury can be systematically linked to specific patterns of diffuse white matter tract damage, as measured by diffusion tensor imaging based fiber tract tracings.

In collaboration with Dr. Sue Swedo of NIMH, Dr. Casey will be imaging children with chronic and episodic OCD relative to normal controls on a task that requires the subject to shift out of a behavioral set in favor of a new one (Casey et al 2002). This two-year NIH intramural contract uses a task that taps frontostriatal and fronto-hippocampal circuitry implicated in OCD developed by Dr. Casey and published in J Neuroscience this past year.

## **Grants and Collaborations**

The Institute directly and in collaboration with others has grants and awards from NSF, NIMH, NIDA, the James S. McDonnell Foundation, the John Merck Fund, and McNeil Health Care Co. This funding supplements the growing endowment from the Mortimer Sackler family.

Dr. Casey has been awarded an R21 from NIDA to pursue brain-imaging studies on the development of prediction and reward circuitry and has received funding from the John Merck Fund to direct a 3<sup>rd</sup> summer institute on the Biology of Developmental Disabilities. She currently has a third R01 pending on Brain Development following Institutionalization in addition to 2 R01s and 1 project on a NIMH Program Project.

Dr. Bruce McCandliss has received funding from the McDonnell Foundation in collaboration with the Brain Trauma Foundation and UC-Berkeley to examine frontocerebellar circuitry with diffusion tensor imaging and functional magnetic resonance imaging in children with cerebellar insults. This grant is in addition to NSF and NIMH funding and a recent scholarship from the John Merck Fund.

Dr. James Swanson has received an NIMH R01 to examine genetic variants of ADHD and has received support from McNeil for a second year of salary and staff support at the Institute.

Dr. Jason Zevin has received a 3-year NRSA from NIH under the mentorship of Dr. Bruce McCandliss to use fMRI to examine the closing of the critical period for non-native speech contrasts in late childhood. This project applies a novel auditory habituation technique to investigate the hypothesis that loss of the ability to learn non-native speech contrasts is systematically related to the acquisition of adult-levels of perceptual expertise in speech perception in an individual's primary language.

Dr. Inge-Marie Eigsti has received a NARSAD to examine orienting and joint attention in autistic children using behavioral and fMRI methods under the co-mentorship of Drs. Myron Hofer, the Director the Sackler Institute at Columbia University and Dr. Casey.

## **Education, Training and Outreach**

As part of the research network mission of the Institute, funded collaborations have been established with Princeton, Yale, Columbia, Duke, UC-Berkeley, Stanford, Brookhaven, Mt. Sinai, U. Penn, UC-Irvine, NIMH, and Oregon. Our current pre- and postdoctoral fellows are from Spain, Norway, U-Penn, Minnesota, the Netherlands, and the College London. Locally, we have formed research collaborations with faculty at the sister Sackler Institute of Columbia and with faculty in the Lasdon Laboratories at Weill Medical College on infant and animal models of brain and behavioral development that complement the Weill Cornell Sackler Institute program of research on human brain development. Finally, this year will mark the first Ithaca/Sackler predoctoral summer fellowships in biomedical research that the Institute has established to form more collaborative ties with students and faculty at the Ithaca campus of Cornell.

The Institute has several training initiatives in addition to the Sackler/Ithaca fellowships for research opportunities for pre- and postdoctoral fellows. These include a third annual summer institute that Dr. Casey has directed with financial support from The John Merck Fund on the Biology of Developmental Disabilities for pre and postdoctoral fellows. In the past, this course has been held at Cold Spring Harbor but will move to Princeton this year and double in size. There will be hands-on workshops in imaging and genetics and lecturers by leading

international experts in developmental psychobiology and neurobiology and the President of Princeton University, Shirley Tilghman, has agreed to give the opening address.

The Institute actively participates in summer workshops with the Functional Neuroimaging Laboratory directed by Drs. David Silbersweig and Emily Stern as part of a Training Grant headed by Dr. Jack Barchas. In addition, Dr. Casey has become an active member of the Neuroscience program at Weill Medical College and is both teaching and sponsoring student rotations and PhD candidates from that program and from the tri-institutional MD PhD program.

Dr. Casey has edited another special issue on developmental psychobiology in the journal Mental Retardation and Developmental Disabilities Research Reviews that parallels the Cold Spring Harbor course lectures from this past summer. Dr. Casey is co-writing a textbook on cognitive developmental neuroscience that is under contract with Oxford Press.

Dr. Posner has begun three new publishing efforts in the area of attention and brain development. First, he has a project with APA books to edit a series of books on Human Brain Development. Second, he has a project with Guilford Press to edit a book on Attention. Finally, together with Dante Cichetti he is co-editing a special issue of Development and Psychopathology on human brain development from a cognitive neuroscience perspective.

Dr. Worden has been working on software tools that serve two important functions. The first allows training of children and adults to be still in the scanning environment by use of feedback from the video display to aid suppression of movements. The second involves tools for visualization of EEG and fMRI data that can be made available to researchers through our website. In addition, he has helped make behavioral assays by Institute affiliated faculty available through our website.

Dr. McCandliss continues to direct one of three networks supported by the Paris based Organization for Economic Cooperation and Development (Center for Research in Education Innovation). The networks will work to develop international cooperation on the collection, organization and dissemination of material on brain mechanisms related to education. The second meeting of the three networks was held in Boston this year. Dr. McCandliss is currently working with OECD on a world-wide initiative to improve literacy and numeracy education. He is developing web sites designed to provide an interactive environment for testing education innovations.

### **Published papers and In Press Papers July 2002-03**

Albright, T.D., Jessell, T.M., Kandel, E.R. & Posner, M.I. (2002). Progress in the neural sciences in the century after Cajal. In P.C. Marjivan (ed.) Cajal and Consciousness: Ann of NY Acad of Sciences, 929.

Brodkin, E.S. Goforth, S.A., Keene, A.H. Fossella, J.A. & Silver, L.M. (2002). Identification of quantitative trait loci that affect aggressive behavior in mice. J. of Neuroscience 22, 1165-1170.

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Casey, B.J., Durston, S., Tottenham, N., Eigsti, I.-M., Galvan, A., Davidson, M.C. & Fossella, J. (In Press). Disruption of Frontostriatal Circuitry, Dopamine and Cognitive Control in ADHD. To appear in D.Barch (Ed.), Cognitive and Affective Neuroscience of Psychopathology. Oxford Press.

Casey, B.J., Tottenham, N. & Fossella, J. (2002). Clinical, lesion, imaging and genetic approaches to the study of inhibitory mechanisms of attention. Developmental Psychobiology. 40:237-254.

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Clarkin, J. & Posner, M.I. (In Press). Defining the mechanisms of borderline personality disorder. Psychopathology

Davidson, M.C., Thomas, K.M., Casey, B.J. (In Press). Imaging the developing brain with fMRI. Mental Retardation and Developmental Disabilities.

Diamond, A., Munakata, Y. & Casey, B.J. (under contract). Cognitive Developmental Neuroscience: A Textbook.

Durston, S., Thomas, K.M., Worden, M.S., Yang, Y., Casey, B.J. (2002). An fMRI study of the effect of preceding context on inhibition. Neuroimage, 16:449-453.

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Durston S: A Review of the Biological Bases of ADHD: What have we learned from imaging studies? Ment Retard Dev Disabil Res Rev, In Press.

Eigsti, I.M., and Shapiro, T. (In Press). Mental Retardation and Developmental Disabilities Research Review.

Fan, J., Flombaum, J.I., McCandliss, B.D., Thomas, K.M. & Posner, M.I. (In Press). Cognitive and Brain Mechanisms of Conflict. Neuroimage

Fan, J., Fossella, J., Sommer, T., Wu, Y., Posner, M. (In Press). Mapping the genetic variation of executive attention onto brain activity. PNAS

Fan, J., McCandliss, B.D., Sommer, T., Raz, M. & Posner, M.I. (2002) Testing the Efficiency and Independence of Attentional Networks. J. Cog. Neuroscience, 14:3 340-347

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Fan, J., Wu, Y., Fossella, J. & Posner, M.I. (2001). Assessing the heritability of attentional networks. BioMed Central Neuroscience, 2:14

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McCandliss, B.D. (In Press). Brain based education. In J. Guthrie (Ed.) 2003 Encyclopedia of Education, Second Edition, New York: Macmillan Reference: New York.

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McCandliss, B.D., Sandak, R., Beck, I., & Perfetti, C., (2003). Focusing attention on decoding for children with poor reading skills: Design and preliminary tests of the Word Building intervention. Scientific Studies of Reading. 7(1),75-105.

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McCandliss, B. D., Fiez, J. A., Protopapas, A., Conway, M., & McClelland, J. L. (In Press). Success and failure in teaching the [r]-[l] contrast to Japanese adults: tests of a Hebbian model of plasticity and stabilization in spoken language perception. Cognitive, Affective, and Behavioral Neuroscience.

McCandliss, B. D., Noble, K. (In Press-2003) The Development of Reading Impairment : a Cognitive Neuroscience Model. Mental Retardation and Developmental Disabilities Research Reviews.

McClelland, J.L., Fiez, J.A., & McCandliss, B.D., (In Press). Teaching the Non-Native [r]-[l] Speech contrast to Japanese adults: training methods, outcomes, and neural basis. Physiology and Behavior.

Posner, M.I. (In Press) The Achievements of Brain Imaging: Past and Present to appear in N. Kanwisher & J. Duncan (eds) Attention and Performance XX. Oxford University Press

Posner, M.I. (In Press) Higher Perception an overview (Oct) To appear in J. Pomerantz editor Neurobiology of Perception and Communication: From Synapse to Society the IVth De Lange Conference. Cambridge UK:Cambridge University Press

Posner, M.I. & Fan, J. (In Press). Attention as an organ system. In Roland Baddeley, Peter Hancock, and Peter Foldiak (Ed.), Information Theory and the Brain. Cambridge University Press.

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Raz, A., Fossella, J., Fan, J., Sommer, T., McGuinness, P., Zephrani, Z., Posner, M. (In Press). Correlates and Exploratory Genetic Associations of Attentional and Hypnotic Phenomena. Hypnose und Kognition.

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Volkow, N.D., Wang, G-J., Fowler, J.S., Logan, J., Franceschi, D., Maynard, L., Ding, Y-S., Gatley, S.J., Gifford, A., Zhu, W., Swanson, J.M. (2002). Relationship Between Blockade of Dopamine Transporters by Oral Methylphenidate and the Increases in Extracellular Dopamine: Therapeutic Implications. Synapse, 43:181-187.

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Worden, M., Noll, D. and Schneider, W. (In Press). Relation Between Stimulus Features And The Expression Of Spatial Attention In Human Areas V1 And V2. NeuroImage.

### **Abstracts/Presentations 2002-2003:**

Institute affiliated faculty have over 100 presentations and abstracts available upon request.

### **Awards and Honors 2002-2003**

B.J. Casey	NIDA R21
B.J. Casey	The John Merck Fund
B. McCandliss	McDonnell Foundation
J. Swanson	NIMH R01
J. Zevin	NIMH NRSA award
I-M Eigsti	NARSAD Young Investigator Award
M.I. Posner	Honorary Doctoral Degree University of Paris