

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

July 2002-July 2003

During this fourth year of the Institute's development we have reached a mature state and are seen internationally as important contributors to research, training and application in the overall field of human brain development. We also have developed close ties with the new Sackler Institute at Columbia whose work involves early development and particularly animal models.

On October 1, 2002 leadership of the Institute will be transferred to Dr. B.J. Casey. Dr. Posner will retire and continue to work on Institute projects from his home in Eugene Oregon. Dr. Casey has been involved in the development of the Institute from its inception and will continue to develop and enlarge the major themes of the Institute. Dr. James Swanson will be continuing his association with the Institute through a generous grant from the McNeil Health Products Corporation. Dr. Kathleen Thomas will be taking up a new appointment as Asst. Prof. in the Department of Psychology at the University of Minnesota.

During the past year we have carried out and published empirical articles using the methods of brain scanning, genetics, high density EEG, training, eye movements and performance studies, to study populations from birth to adulthood. We have developed a summer course for the training of researchers and have edited several compendia of articles informing researchers about new developments in this field. We continue to develop a wide network of collaborating institutions in the US and abroad.

RESEARCH

1. Development of Control Mechanisms

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

We have traced the emergence of the ability of infants to control their performance in a go-nogo task. Children of 36-38 months do not show the ability to execute an instruction given by one animal while inhibiting the instruction when made by another animal nor do they give evidence of detecting their errors, but at 39-41 months they do show both of these (Jones, Rothbart & Posner, in press).

We now have findings that provide clues for the neural basis of this type of inhibitory control. We show developmental differences in brain activity in children relative to adults both cortically and subcortically. First, we showed greater activity of association cortex (e.g. prefrontal cortex) in children (6 to 11 year olds) relative to adults when overriding an inappropriate response but no differences in activity of sensorimotor cortex (Durston et al., submitted). Second, we showed that when learning a

new behavior that requires overriding an old one, both striatal and hippocampal regions are recruited by children and adults. Children, however show less focal activations in these areas, with activity extending ventrally and anteriorly for them relative to adults (Casey et al., submitted). A focal pattern of activity appears to coincide with mature cognitive controls in fronto-striatal and hippocampal circuitry.

In adult work we have shown that the ability to resolve conflict in three quite different tasks (Stroop, Simon and Flanker) activate a common neural network of lateral prefrontal cortex and anterior cingulate areas (Fan et al., in press)

Our studies using the Child Attention Network Task (ANT) show that this conflict resolution network develops up to seven years of age (Fan et al., submitted). Development continues in the ability to prepare for a target (alerting network) at least until adolescence (Fan et al., submitted). At 30 months tasks using key presses to indicate the resolution of conflict correlates with the ability to make eye movements toward ambiguous targets. This finding suggests that we can use eye movements to trace the precursors of conflict resolution even in early infancy (Rothbart, Ellis & Posner, in press).

Another control system is fear. In adults this is often indexed by amygdala activity. The classic adult amygdala response is not fully developed in middle childhood and early adolescence (Thomas et al., 2001). In addition, children with anxiety disorders show an exaggerated amygdala response that looks more like the adult response, while children with depression showed a blunted amygdala response to faces.

2. Genomics

We have developed a genomics laboratory in conjunction with Prof. Donald Pfaff at Rockefeller University. Recently, John Fossella who directs our effort there has been awarded an NRSA fellowship and a NARSAD Young Investigator Award. During this year Fossella and associates of the Institute have:

Provided evidence on the heritability of attention network using the ANT (Fan et al., 2001)

Laid out a strategy for investigation of the genetics of normal attention (Fossella et al., 2002) and found evidence of the role of 4 genes in control of the conflict network. (Fossella et al. submitted).

Found evidence of the relation of genes to brain morphometry in neuroimaging studies (Casey et al., 2001).

Dr. 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 (Swanson et al., 2001). He has developed a collaboration with the National Human Genome Research Institute (NHGRI) to perform a genome scan of ADHD children and controls. A large number of families from the multiple clinical trials performed over the past few years to develop new medications for ADHD will be recruited in the new study.

The UCI group has sequenced the DRD4 gene and related variation in DNA from ADHD cases to variation in DNA from the worldwide human population (Ding et al, 2002).

3. Training Studies

A major aspect of the research of the Institute lies in the development of training as a method of probing mechanisms of learning in the human brain and as a means of providing treatment for disorders.

Dr. Worden in collaboration with Mariano Sigman at Rockefeller University have examined the development of implicit learning in the visual system. They used recordings from scalp electrodes to show that small changes can be seen at a very early stage of visual processing after practice. These effects cascade into much larger effects at somewhat later stages of processing possibly reflecting mechanisms of automatic capture of attention by the trained stimuli.

Dr. Amir Raz and a group of researchers in Finland report in *Nature* the first convincing evidence of language related learning during sleep for new-born infants.

We have examined the development of sequence learning in infants, children and adults. It appears as though the learning to orient to single unambiguous locations develops by four months (Clohessy et al., 2001) and shows little change until adulthood (Posner, 2001). However, the complexity of associations and ability to use explicit information shows strong development in later childhood (Thomas & Nelson, 2001). Thomas is currently comparing eye movement and key press response in sequence learning experiments.

Dr. McCandliss and colleagues (in press) have demonstrated improvements in reading skill in children can be boosted in sounding out words and in comprehension by two grade levels after only 20 sessions. He has developed programs to implement this method by computer and he is starting studies in the New York public schools testing the method further.

Work on attention training programs for use by preschool and elementary school children has been progressing and evaluation of these methods in human and animal studies is currently underway.

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, ADHD, 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.

Dr. Amir Raz together with Dr. Theodore Shapiro and associates (Raz & Shapiro, 2002; Raz et al., in press) have examined how hypnotism alters processing by the human brain. They found

that the hypnotic instruction to see stimuli as nonsense material eliminated the Stroop effect in highly hypnotizable subjects while having no effect on low hypnotizables. Preliminary results of imaging studies suggest that the instruction leads to a reduction of activation in the anterior cingulate during the Stroop task for high hypnotizables.

Dr. Swanson has made progress in diagnosis, and pharmacological treatment of ADHD (Swanson et al., 2001). His work in this area focused 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 2001; 2002)

In collaboration with Drs. Otto Kernberg, John Clarkin and David Silbersweig we have been developing an approach to the biology of borderline personality disorder. We are examining candidate genes and are working with Dr. Silbersweig to image networks related to the disorder both before and after therapy. A overview of our strategy for the study of personality disorders has been submitted to Development and Psychopathology (Posner, et al, submitted).

Grants and Collaborations

Dr. Casey has been awarded a second RO1 by NIMH to pursue brain imaging studies on early diagnosis of ADHD.

Dr. John Fossella received NRSA and NARSAD awards for his studies of genes and attention.

Drs . Bruce McCandliss and M.I. Posner received a five-year project award within the Learning Disabilities Center at Yale University.

Dr. Bruce McCandliss has received the Merck Scholar award in Cognitive Science. This will provide four years of support at \$60,000 per year.

The McNeil Health Care Company provided support of \$200,000 per year for three years to allow James Swanson to work half time at the Institute

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

Training and Outreach

Dr. Casey has become an active member of the Neuroscience program at Weill Medical College and is sponsoring student rotations.

Four compendia updating researchers on new development in the field of human brain development have appeared in 2001 or are about to appear this year. Two are edited by Dr. Casey and include a special issue of *Developmental Psychobiology*, which summarizes current methods in the field and a special issue of *Developmental Science* on Pediatric Neuroimaging. Dr. Posner and associates have edited a report on research opportunities in human brain development, which appeared as a special issue of *Developmental Science*. The meeting of the ARNMD held in 2000 appeared as two special issues of *Clinical Neuroscience Research* edited by Dr. Posner.

Dr. Casey and members of the institute will be involved with a training course at Cold Spring Harbor supported by the John Merck Fund. This course is limited to 20 international fellows and targeted for upper graduate students and postdoctoral fellows in psychology, neuroscience, and related disciplines (See <http://nucleus.cshl.org/meetings/CourseInfo.htm>)

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.

Dr. McCandliss has been chosen to head 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 first meeting of the networks will be held in London at the end of April 2002.

Published papers and In Press Papers July 2001-02

Albright, T.D., Jessell, T.M., Kandel, E.R. & Posner, M.I. Progress in the neural sciences in the century after Cajal. In P.C. Marijuan(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

Casey, B.J. Fossella, J. & Yeung, N. (in press). Role of the Anterior Cingulate Cortex in Cognition and Emotion. To be published in V.S. Ramachandran (Ed.) *Encyclopedia of the Human Brain*. Academic Press: San Diego, CA.

Casey, BJ and de Haan, M (2002) Special Issue on "Neuroimaging Methods in Developmental Science", Invited Editor, *Developmental Science*

Casey, BJ and Munakata Y (2002) Special Issue on "Converging Methods Approach in Developmental Science", Invited Editor, *Developmental Psychobiology*.

Casey, B.J., Forman, S.D., Franzen, P., Berkowitz, A., Braver, T.S., Nystrom, L.E., Thomas, K.M. & Noll, D.C. (2001). Sensitivity of prefrontal cortex to changes in target probability: A functional MRI study. Human Brain Mapping. 13-26-33.

Casey, B.J., Durston, S. & Fossella, J. (2001). A Mechanistic Model of Cognitive Control: Clinical, Neuroimaging, and Lesion Studies. Clinical Neuroscience Research.1, 267-282.

Casey, B.J., Davidson, M. & Rosen, B. (in press). The Basics of fMRI and its application to developmental science. Developmental Science.

Casey, BJ, Tottenham, N. & Fossella, J. (in press). Clinical, lesion, imaging and genetic approaches to the study of inhibitory mechanisms of attention. Developmental Psychobiology.

Casey, BJ, Thomas, KM, Davidson, MC, Kunz, K & Franzen, PL (submitted 2/02). Dissociating Striatal and Hippocampal Function Developmentally with a Stimulus-Response Compatibility Task.

Casey, B.J., Thomas, K.M., & McCandliss, B.D. (2001). Applications of magnetic resonance imaging to the study of development. In C.A. Nelson & M. Luciana (Eds.), *Handbook of Developmental Cognitive Neuroscience*, pp. 137-148. MIT Press: Cambridge, MA.

Casey, B.J., Yeung, N. & Fossella, J. (2002) Role of the anterior cingulate cortex in behavior. *Encyclopedia of the Human Brain*. Academic Press: SanDiego

Cheour M, Martynova O, Naatanen R, Erkkola R, Sillanpaa M, Kero P, Raz A, Kaipio, ML, Hiltunen J, Aaltonen O, Savela J, Hamalainen H (2002) Speech sounds learned by sleeping newborns. *Nature* 415 (6872): 599-600

Clohessy, A.B., Posner, M.I. & Rothbart, M.K. (2001) Development of the functional visual field. *Acta Psychologica* 106, (1-2), 51-68.

de Haan, M. & Thomas, K.M. (in press). Application of ERP and fMRI to developmental science. *Developmental Science*.

Diamond, A., Munakata, Y. & Casey, BJ (in preparation) Cognitive Developmental Neuroscience: A Textbook.

Ding Y-C, Chi H-C, Grady DL, Morishima A, Kidd JR, Kidd KK, Flodman P, Spence MA, Schuck S, Swanson JM, Zhang Y-P, Moyzis RK. (2002). Evidence of positive selection acting at the

Durston S., Hulshoff Pol H.E., Casey B.J., Giedd J.N., Buitelaar J.K., Van Engeland H (2001) Anatomical MRI of the developing human brain: What have we learned. Journal of the American Academy for Child and Adolescent Psychiatry. 40:1012-1020.

Durston, S., Thomas, K.M., Worden, M.S., Yang, Y., Casey, B.J. (in press). An fMRI study of the effect of preceding context on inhibition. Neuroimage.

Durston, S., Thomas, K.M., Yang, Y., Ulug, A.M., Zimmerman, R.D. & Casey, B.J. (submitted 1/02). An fMRI study of the effect of preceding context on inhibition.

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

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

Fan, J., Rueda, M.R., Halparin, J., Gruber, D., Papert-Lercari L.P., McCandliss B.D. & Posner, M.I. (submitted) Assessing the development of attentional networks in six to ten year old children.

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

Fernandez Duque, D. & Posner, M.I. (2001) Brain imaging of attentional networks in normal and pathological states. *J. of Clinical and Experimental Neuropsychology* 23 (1) 74-93.

Fossella, J., Posner, M.I., Fan, J., Swanson, J.M. & Pfaff, D.M. Attentional Phenotypes and higher mental function (2002) The Scientific World Journal 217-223

Fossella, J., Sommer, T., Fan, J., Wu, Y.H., Swanson, J.M., Pfaff, D.W. and Posner M.I., (2002) (submitted) Assessing the Molecular Genetics of Attention Networks

Harm, M. W., McCandliss, B. D., & Seidenberg, M. S., (accepted pending revisions). Modelling the Successes and Failures of Interventions for Disabled Readers. Scientific Studies of Reading.

Jones, L., Rothbart, M.K. & Posner, M.I. Development of inhibitory control in three year old children (in press) Developmental Science

McCandliss, B.D., Beck, I., Sandak, R., & Perfetti, C. (in press). Focusing attention on decoding for children with poor reading skills: A study of the Word Building intervention. Scientific Studies of Reading.

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*.

Nikolaev, A.R., Ivanitsky, G.A, Ivanitsky, A.M., Posner, M.I. & Abdullaev, Y.G. (2001) Short-term correlation between frontal and Wernicke's areas during word association: an event-related potential analysis in human subjects. *Neurosci Lett.* 298,107-110.

Posner, M.I. Educating the human brain: a commentary (2001) in J. McClelland and R. Siegler eds *Mechanisms of cognitive development: behavioral and neural perspectives.* Hillsdale N.J.:LEA Ch. 16, 387-399.

Posner, M.I. (2001) Normal and pathological development of the nervous System. *Clinical Neuroscience Research* 1 (3) 173-174

Posner, M.I (2001) Developing Brains: the work of the Sackler Institute. *Clinical Neuroscience Research* 1 (4) 258-266

Posner, M.I. (2001) Cognitive neuroscience and the synthesis of brain and mind. In E. Dupoux (ed) *Language, brain and cognitive development. Essays in honor o Jacques Mehler.* Cambridge Mass:MIT Press 403-416

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 Systems 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. & Halparin, J.D. (2001) A review of: *The executive brain: Frontal lobes and the Civilized Mind* by E. Goldberg, *Nature Medicine* 7/7 767-768

Posner, M.I. & Rothbart, M.K. (2001) The neuroeducation of Nico, A review of A.M. Battro *Half a Brain is Enough Cerebrum* 3/2 91-95

Posner, M.I. Rothbart, M.K. Farah, M.J., & Bruer, J. eds (2001) *Human Brain Development. Developmental Science* 4/3

Posner, M.I., Rothbart,M.K. & Gerardi-Caulton, G. (2001) Exploring the biology of socialization. In A.R. Damasio et al (eds) *The Conergerence of Natural and Human Sciences Ann. of the New York Academy of Sciences* 935 208-216

Posner, M.I. & Rothbart, M.I.(2001) *The Human Brain and Attention to School Subjects* in Elisa Frauenfelder& Flavia Santoianni (eds) *Psychoeducational Sciences: Research Perspectives*

Posner, MI, Rothbart, MK, Vizueta, N., Thomas, K.M., Levy,K., Fossella, J., Silbersweig,DA, Stern, E., Clarkin, J., & Kernberg, O. (submitted) *An approach to the psychobiology of personality disorders. Development and Psychopathology*

Posner, M.I. & Rueda, M.R. (in press) Mental chronometry in the study of individual and group differences. *J. Clinical and Experimental Neuropsychology*

Raz, A. and Shapiro, T. (2002) Hypnosis and neuroscience - A cross talk between clinical and cognitive research *Archives of General Psychiatry* 59 (1) 85-90

Raz, A, Shapiro, T., Fan, J. & Posner, M.I. (in press) Hypnotic suggestion and the modulation of stroop interference. *Archives of General Psychiatry*

Rothbart, M.K., Ellis, L. & Posner, M.I. (in process) Developing mechanisms of temperamental self regulation. *J. of Personality*

Rothbart, M.K., & Posner, M.I. (2001) Mechanisms and variation in the development of attentional networks in C.A. Nelson & M. Luciana eds The Handbook of Developmental Cognitive Neuroscience. Cambridge Mass.:MIT Press Ch. 24, 353-363

Swanson, J. Deutsch, C., Cantwell, D., Posner, M., Kenndy, J., Barr, C., Moyzis, R., Schuck, S., Flodman, P & Spence, A. Genes and attention-deficit hyperactivity disorder et al (2001) *Clinical Neuroscience Research*. 1 (3) 207-216

Swanson J, Lerner M, Gupta S, Shoulson I, Wigal S. Development of a New Once-A-Day Formulation of Methylphenidate of the Treatment of ADHD: Proof of Concept and Proof of Product Studies. General Psychiatry, In Press, 2002.

Swanson JM, Lerner M, Steinhoff K, Wigal S. (2001). Methylphenidate (OROS Formulation)-A Viewpoint. CNS Drugs, 15(6):502-503.

Swanson JM, Kraemer HC, Hinshaw, SP, Arnold, LE, Conners, CK, Abikoff, HB, Clevenger W, Davies M, Elliott, G, Greenhill, LL, Hechtman, L, Hoza, B, JJensen, PS, March, JS, Newcorn JH, Owens L, Pelham, WE, Schiller E, Severe, J, Simpson S, Vitiello, B, Wells, CK, Wigal, T, Wu, M. (2001). Clinical Relevance of the Primary Findings of the MTA: Success Rates Based on Severity of ADHD and ODD Symptoms at the End of Treatment. J. Amer. Acad. Child & Adolesc. Psychiatry, 40(2): 168-179.

Swanson JM, Posner M, Wasdell M, Sommer T, Fan J. (2001). Genes and Attention Deficit Hyperactivity Disorder. Current Psychiatry Reports, 3: 92-100.

Swanson JM, Volkow N. Pharmacokinetic and pharmacodynamic properties of stimulants: implications for the design of new treatments for ADHD. Behavioural Brain Research, In Press, 2002

Swanson JM, Volkow N. (2001). Pharmacokinetic and Pharmacodynamic Properties of

Methylphenidate in Humans. In M.V. Solanto, A.F.T. Arnsten, F.X. Castellanos. (Eds.), Stimulant Drugs and ADHD: Basic and Clinical Neuroscience, (pp. 259-282). Oxford University Press.

Thomas, K. M. & Casey, B. J. (in press). Methods for imaging the developing brain. In M. de Haan & M. H. Johnson (Eds.), *The Cognitive Neuroscience of Development*.

Thomas, K. M., & Nelson, C. A. (2001). Serial reaction time learning in preschool- and school-age children. *Journal of Experimental Child Psychology*. 7(9) 364-387

Thomas, K.M., Drevets, W.C., Whalen, P.J., Eccard, C.H., Dahl, R.E, Ryan, N.D. & Casey, B.J. (2001). Amygdala response to facial expressions in children and adults. Biological Psychiatry. 49: 309-316.

Thomas, K.M., Drevets, W.C., Dahl, R.E., Ryan, N.D., Birmaher, B., Eccard, C.H., Axelson, D., Whalen, P.J., & Casey, B. J. (2001). Abnormal amygdala response to faces in anxious and depressed children. Archives of General Psychiatry, 58: 105-1063.

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

Worden, M., Martinez, A & Posner, M.I.(in press) Neural basis of spatial attention. *Encyclopedia of Cognitive Science*

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

Awards and Honors

J. Fossella NARSAD Young Investigator Award

K. Thomas K award (five years of support)

Bruce McCandliss, Merck Award in Cognitive Science.

Amir Raz DeWitt Wallace Readers Digest Award

Michael Posner Honorary Degree Nottingham July 2002