

Division of Integrative Neuroscience

1. Overview

The Division of Integrative Neuroscience is a research division aimed at understanding the pathophysiology underlying psychiatric illnesses using approaches that span multiple levels of neurobiological analysis. Accordingly, we combine molecular and cellular neurobiological techniques with analyses of the behavior of neural circuits and neural systems in order to fully understand animal models of psychiatric illnesses such as anxiety disorders and schizophrenia. Consisting of three main research programs (laboratories led by Dr. Rene Hen, Dr. Holly Moore, and Dr. Joshua Gordon) and several additional faculty members and fellows, Integrative Neuroscience maintains close ties with the Center for Neurobiology and Behavior and various other neuroscience laboratories in the department.

2. Staff

René Hen	Professor
Joshua Gordon	Assistant Professor / Psychiatrist
E. David Leonardo	Assistant Professor / Psychiatrist
Holly Moore	Assistant Professor
Alex Dranovsky	Assistant Professor / Psychiatrist
Mark Opler, PhD	Assistant Professor
Victoria Cressman	Assistant Professor
Amar Sahay	Research Scientist
Michael Drew	Research Scientist
Mark Alter	Research Fellow / Psychiatrist
Susanne Ahmari	Research Fellow / Psychiatrist
Collin O'Carroll	Research Fellow
Kenji Tanaka	Research Fellow / Psychiatrist
Nesha Burghardt	Research Fellow
Salomao Segal	Research Fellow
Torfi Sigursson	Postdoctoral Research Scientist

3. Highlights

- 1: Sahay A, Hen R. Adult hippocampal neurogenesis in depression. *Nat Neurosci.* 2007; 10(9):1110-5.
- 2: Holick KA, Lee DC, Hen R, Dulawa SC. Behavioral Effects of Chronic Fluoxetine in BALB/cJ Mice Do Not Require Adult Hippocampal Neurogenesis or the Serotonin 1A Receptor. *Neuropsychopharmacology.* 2007.
- 3: David DJ, Klemenhagen KC, Holick KA, Saxe MD, Mendez I, Santarelli L, Craig DA, Zhong H, Swanson CJ, Hegde LG, Ping XI, Dong D, Marzabadi MR, Gerald CP, Hen R. Efficacy of the MCHR1 antagonist N-[3-(1-[4-(3,4-difluorophenoxy)phenyl]methyl)(4-piperidyl))-4-methylphenyl]-2-methylpropanamide (SNAP 94847) in mouse models of anxiety and depression following acute and chronic administration is independent of hippocampal neurogenesis. *J Pharmacol Exp Ther.* 2007; 321(1):237-48.
- 4: Saxe MD, Malleret G, Vronskaya S, Mendez I, Garcia AD, Sofroniew MV, Kandel ER, Hen R. Paradoxical influence of hippocampal neurogenesis on working memory. *Proc Natl Acad Sci U S A.* 2007; 104(11): 4642-6.

4. Current Research

HEN LAB

René Hen's research is focused on the contribution of serotonin (5-HT) receptors to pathological states such as depression and anxiety. Pharmacological studies and molecular cloning have identified several subtypes of receptors with distinct properties, signaling systems, and tissue distributions. However, the study of the function of individual serotonin receptor subtypes has been hampered by the lack of specific drugs. In addition, a number of the serotonergic drugs that are active in the treatment of neuropsychiatric disorders influence the whole serotonergic system. For example, antidepressants such as fluoxetine are 5-HT uptake blockers and potentiate the action of 5-HT at multiple post-synaptic sites. To dissect the contributions of individual serotonin receptors to physiology and behavior, mouse mutants lacking individual receptor subtypes were created in his laboratory, providing genetic models for a number of

human behavioral traits such as impulsiveness, depression, and anxiety. Tissue specific and conditional knockouts are currently being used to identify the neural circuits underlying these traits. Recently his lab has also been investigating the function of the ventral hippocampus and the contribution of hippocampal neurogenesis to mood and cognition. Specifically, they have shown that antidepressants stimulate the division of neuronal progenitor cells in the dentate gyrus, which in turn results in an increase in the number of immature neurons in the adult hippocampus. Furthermore, using various ablation strategies they have shown that hippocampal neurogenesis is required for some of the behavioral effects of antidepressants. Novel antidepressant therapies aimed at targeting directly hippocampal stem cells are currently under investigation.

GORDON LAB

The Gordon lab studies mouse genetic models of psychiatric diseases from an integrative neuroscience perspective, focused on understanding how a given disease mutation leads to a behavioral phenotype in disease-related mouse models. A major effort in the laboratory is aimed at identifying the effects of a deletion in the serotonin 1A-receptor (5-HT1AR) that lead to a phenotype of increased anxiety-related behavior. We have identified cell anatomical and functional abnormalities in the hippocampus of 5-HT1AR knockouts. These data argue that hippocampal dysfunction plays a role in the anxiety-related phenotype in 5-HT1AR-deficient mice. Current efforts include further characterization of the nature of hippocampal activity differences using multiple single-unit recordings, as well as attempts to prove causality by artificially altering hippocampal activity. In addition, in collaboration with Dr. Lorna Role, we have begun to examine ventral striatal activity in neuregulin-1 (NRG-1) heterozygote animals. NRG-1 has been identified as a schizophrenia-predisposition gene in several independent studies, and mice lacking a single copy of the gene have several behavioral hallmarks of schizophrenia. We have identified abnormal patterns of activity in the ventral striatum of these mice, and are currently characterizing this activity and attempting to determine its behavioral relevance. Finally, in a collaboration with Drs. Joseph Gogos and Maria Karayiorgou, we have begun to examine hippocampal and medial prefrontal cortex activity in mice carrying a genetic deletion homologous to one which causes schizophrenia in humans.

Recent publications:

Gordon, J.A., Hen, R. (2006). TREKING toward new antidepressants. *Nature Neuroscience* 9:1081-1083.

Klemenhagen, K.C., **Gordon, J.A.,** Hen, R., and Gross, C.T. (2006). Increased fear response to contextual cues in mice lacking the 5-HT1A receptor. *Neuropsychopharmacology* 31:101-111.

MOORE LAB

The Moore laboratory conducts several inter-related lines of research: These are broadly described as 1) developmental changes in cerebral cortical regulation of limbic basal forebrain and ascending monoaminergic systems during adolescence, 2) the neural and behavioral consequences of specific disruptions of cerebral cortical development in rodents as models of the neuropathology of schizophrenia, and 3) limbic circuit mechanisms relevant to specific therapeutic, diagnostic or research procedures used in psychiatric patients. To pursue these lines of research, we use anatomical, *in vivo* neurochemical and neurophysiological and behavioral techniques. Description of the progress made during the 2006-2007 year is as follows:

Ontogeny of corticolimbic circuits. We have completed the initial phase of a study of the developmental changes in dendritic morphology of hippocampal neurons. The hippocampal complex, parahippocampal cortex, prefrontal cortex, and "limbic-related" regions of the basal forebrain and midbrain, including medial basal ganglia, amygdala, medial thalamus, and hypothalamus form multiple overlapping circuits that operate dysfunctionally in many psychiatric disorders. Moreover, many such disorders, including anxiety, addiction disorders and schizophrenia, emerge in most individuals during adolescence or early adulthood. Thus, it is imperative to understand how these circuits are changing as the individual matures from early adolescence to adulthood. We have completed initial phases of two studies showing significant remodeling of limbic circuits during adolescence in the rat. The first study has shown that during adolescence, the density of dendritic spines on projection neurons of the subiculum, the major output region of the hippocampal complex, change significantly (Parisot et al., 2006). We are currently determining if this morphological change relates to changes in the inputs to these neurons from the hippocampus, prefrontal cortex and other regions. An another study, using retrograde tract-tracing techniques, we have observed that cortical and thalamic inputs to the amygdala undergo marked pruning during early and late adolescence, respectively (Cressman et al., 2007). The amygdala is involved in fear, anxiety and maladaptive stimulus-response habits; thus, these structural changes in the inputs to the amygdala during adolescence may

underlye the progressive increase in risk for anxiety and addiction disorders during adolescence. We are following up these studies with functional assessments of these circuits using electrophysiological and behavioral techniques.

Rodent models of the pathophysiology of schizophrenia. Dr. Moore's studies have determined a specific window around embryonic day 17 in the rodent, during which methylation (specifically, abnormal alkylation) of nucleic acids causes altered development of the cortical and thalamic subregions that are particularly relevant to schizophrenia. Specifically, in utero exposure of the rodent embryo on embryonic day 17 to methylazoxymethanol acetate (MAM) produces a cortical neuropathology, abnormal dopamine transmission, and cognitive deficits observed in schizophrenia patients (Moore et al 2006). Importantly, this model also features abnormal behavioral and neurochemical changes occurring during the transition from puberty to adulthood that may model the "peripubertal" period of risk. Thus the MAM E17 model will be used to identify early and peripubertal neurobehavioral developmental processes that may be highly sensitive to etiologic factors in schizophrenia. During the past year, the Moore laboratory has pursued examined neurophysiological mechanisms underlying abnormal cognitive and psychosis-relevant behaviors in this model. In collaboration with Dr. Scott Small, we have applied a functional imaging method identical to that used to study patients. We have observed that, like schizophrenia patients, MAM E17 rats show hyperactivity within hippocampal circuits (Remole et al., 2007). Further, MAM E17 rats show an abnormal functional coupling between hippocampal subregions. In parallel, we have shown that the morphology of the neurons in the CA1 and subicular subregions of the hippocampus is abnormal. These studies are, thus beginning to characterize candidate mechanisms underlying the psychosis-related hippocampal hyperactivity in schizophrenia. We have also examined molecular mechanisms underlying the preferential maldevelopment of limbic-related cortical circuits by MAM E17 exposure. We have found that expression of genes related to DNA repair, neurite development and specific ion conductances on neuronal membranes are disrupted by MAM E17 exposure. The findings are consistent with abnormalities the neuronal morphology and neurophysiological activity of specific cortical regions in this model.

The Moore laboratory also studies a number of genetic mouse models with schizophrenia-related neural or psychopathology. The hippocampal activity and the responsivity of behavior and the mesolimbic DA system to amphetamine are inter-related phenotypes highly relevant to schizophrenia. The MAM E17 shows abnormal increases in both of these phenotypes. Another study initiated this year also shows that the MAM E17 model exhibits higher levels of glutamate and its precursor in the hippocampus and other limbic-related cortical and thalamic regions (Mears et al., 2007). Interestingly, in a mouse model developed by Stephen Rayport, MD at Columbia U., our lab has found that both of these phenotypes are *hyponormal*. This model, the GLS1 heterozygote has a primary deficit in glutamate recycling. The Moore laboratory completed a study on the characterization of glutamate-dopamine interactions in this model, showing a decrease in the response of striatal DA efflux to amphetamine. This may indicate that limiting glutamate synthesis or release may have produce antipsychotic effects (Gaisler-Solomon et al., 2007).

The Moore lab has continued its collaboration with the laboratories of M. Elizabeth Ross and Stewart Anderson at Weill Medical College, Cornell University, to characterize the anatomical, neurophysiological and behavioral abnormalities in two models of cerebral cortical interneuron pathology relevant to schizophrenia. We completed a study showing that the cell cycle gene *cyclin D2* is important for the determination of the parvalbumin (PV)-expressing interneurons in the cortex. *cD2* mutants show a significant loss of PV interneurons and subnormal inhibitory synaptic transmission in the cortex (Glickstein et al., in press). The Moore laboratory has also conducted experiments characterizing striatal dopamine transmission and dopamine-related behaviors in three models of haploinsufficiency of the neuregulin 1 gene (NRG 1), a gene linked to increased risk for schizophrenia and important for both neuronal and glial development. These experiments are included in recent publications by laboratories of Lorna Role and David Talmadge at Columbia U. and Gabriel Corfas at Harvard U. These models can now be used to understand mechanisms by which these genetic molecular pathways or neuronal subpopulations may be altered predispose the brain to dysfunction of the frontal and limbic corticostriatal circuits that are homologous to the circuits affected in schizophrenia.

Recent Publications:

Lavin A, **Moore H**, Grace AA (2005) Prenatal disruption of neocortical development alters prefrontal cortical neuron responses to dopamine in adult rats. *Neuropsychopharmacology*, 30, 1426-1435.
Muller JM, Brunelli SA, **Moore H**, Myers MM, Shair HN (2005). Maternally-modulated infant separation responses are regulated by D2-family dopamine receptors, *Behavioral Neuroscience*, 119, 1384-1388.
Kellendonk C, Simpson EH, Polan HJ, Malleret G, Vronskaya S, Winiger V, **Moore H**, Kandel ER: (2006)

Transient and selective over-expression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortical functioning. *Neuron*, 49, 603-615.

Moore H, Jentsch JD, Ghajarnia M, Geyer MA, Grace AA: (2006) A neurobehavioral systems analysis of the effects of gestational exposure to methylazoxymethanol acetate (MAM) in the rat: implications for the neuropathology of schizophrenia. *Biological Psychiatry*, 60, 253-264.

Meshi D, Drew MR, Ansorge MS, David, D, Saxe M, Santerelli L, Malapani C, **Moore, H**, Hen R., Hippocampal neurogenesis is not required for the effect of environmental enrichment. *Nature Neuroscience*, 9, 729-731.

Journal Articles

Shen L, Nam HS, Song P, **Moore H**, Anderson SA (2006) FoxG1 haploinsufficiency results in impaired neurogenesis in the postnatal hippocampus and contextual memory deficits. *Hippocampus*, 16:875-890.

Roy K, Murtie JC, El-Khodori BF, Edgar N, Sardi SP, Hooks BM, Benoit-Marand M, Chen C, **Moore H**, O'Donnell P, Brunner D, Corfas G (2007) Loss of erbB signaling in oligodendrocytes alters myelin and dopaminergic function, a potential mechanism for neuropsychiatric disorders. *Proceedings of the National Academy of Sciences of the United States of America*. 104:8131-8136.

Glickstein SB, **Moore H**, Slowinska B, Racchumi J, Suh M, Chuhma N, Ross ER (2007) , Selective cortical interneuron and GABA deficits in cyclin D2-null mice, *Development*, 134, 4083-4093.

Schobel SA, Lewandowski, NM, Corcoran C, Pereira AC, Moore H, Tang M, Kimhy D, Brown T, Malaspina D, Small SA, The CA1 subfield is a dominant site of hippocampal hyperfunction in schizophrenia, *submitted*

Published Abstracts.

Cressman V, Parisot N, Moore H (2007) Region-specific remodeling of prefrontal cortical and thalamic inputs to the amygdala during periadolescence in the rat. *2007 Annual Meeting of The Society for Neuroscience, Abstracts, Program/Poster # 37.8.*

Merker R, Krueger K, Chemiakine A, Gingrich J, Moore H (2007) Enhanced amphetamine sensitization of striatal dopamine efflux in the NRG1 Type I/II heterozygote. *2007 Annual Meeting of The Society for Neuroscience, Abstracts, Program/Poster # 59.18*

Gaisler-Salomon I., Miller GM, Chuhma N, Lewandowski NM, Masson J, Ghoddoussi F, Hamon M, Ren R, Sibille E, Moore H, Galloway M, Small SA, Rayport S (2007) Altered hippocampal function and decreased sensitivity to pro-psychotic drugs in glutaminase-deficient mice. *2007 Annual Meeting of The Society for Neuroscience, Abstracts, Program/Poster # 59.24.*

Segal S, Tetens J, Kegeles, Castrillon J, Steinfeld S, Krueger K, Dashnaw S, Hirsch J, Abi-Dargham A, Bradberry CW, Slifstein M, Moore H (2007). The effects of local high frequency electrical stimulation on monoamine efflux in the subgenual cingulate cortex (Brodmann Area 25) and its striatal and thalamic projection regions. *2007 Annual Meeting of The Society for Neuroscience, Abstracts, Program/Poster # 267.22.*

Moore H, Slifstein M, Castrillon J, Tetens J, Kegeles LS, Bradberry CW, Krueger K, Segal S, Hackett E, Scher E, Kambalov O, Duvall M, Steinfeld S, Laruelle M, Abi-Dargham A (2007) Amphetamine-induced changes in [¹¹C]-fallypride specific binding and dopamine efflux are correlated in cortical, striatal and thalamic regions in the primate. *2007 Annual Meeting of The Society for Neuroscience, Abstracts, Program/Poster # 513.11.*

Remole K, Schobel S, Small SA, Moore H (2007) Effects of amphetamine on neuronal activity and regional blood flow in the prepubertal and adult subiculum mice with MAM E17-induced cellular pathology. *2007 Annual Meeting of The Society for Neuroscience, Abstracts, Program/Poster #607.12.*

Mears RP, Galloway MP, Boutros NN, Moore H (2007) Neurochemical phenotype determined by proton magnetic resonance spectroscopy (MRS) in the MAM E17 rodent model of schizophrenia. *2007 Annual Meeting of The Society for Neuroscience, Abstracts, Program/Poster #607.13.*

DRANOVSKY AND LEONARDO LABS

Alex Dranovsky and David Leonardo have embarked on a collaboration to develop novel tools in using the mouse as a model to study the neuro-circuitry of psychiatric disease. They are using molecular biology techniques to generate inducible transgenic mice that will allow manipulations such as reversible inactivation of genetically defined populations of neurons in transgenic mice. These animals will be used to disrupt genetically defined circuits that have been implicated in psychiatric disease and study how altering brain circuits impact on behaviors in animal models of illness.

There are two major areas of emphasis at this time:

- 1) Using circuit inactivation techniques they are investigating the regional aspects of hippocampal function with the hypothesis that dorsal connections help the brain compute cognitive information, while ventral connections compute emotional information.
- 2) Studying the contribution of adult hippocampal neurogenesis to hippocampal structure and function with the hypothesis that adult-born neurons integrate into hippocampal circuitry, change hippocampal connectivity, and ultimately help the hippocampus compute emotional and cognitive information.

5. Awards and Honors

Joshua A. Gordon

Gatsby Initiative in Brain Circuitry Pilot Project Grant

E. David Leonardo

NIH K-Award

Alex Dranovsky

2006 NARSAD Young Investigator Award

NIH K-Award

Michael Drew

2006 NARSAD Young Investigator Award

Amar Sahay

2006 NARSAD Young Investigator Award

Mark Alter

2006 NARSAD Young Investigator Award