

Division of Integrative Neuroscience

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Annual Report for July 1, 2007 – June 30, 2008

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, the Division combines molecular and cellular neurobiological and behavioral techniques with analyses of neural circuits and neural systems to fully understand animal models of psychiatric illnesses such as anxiety disorders, depression and schizophrenia. Consisting of laboratories led by Dr. Rene Hen, Dr. Holly Moore, Dr. Joshua Gordon, Dr. Karen Duff, Dr. Andreas Kottmann, Dr. Peter Balsam and Drs. E. David Leonardo and Alex Dranovsky and several additional faculty members and fellows, Integrative Neuroscience maintains close ties with the Department of Neuroscience and various other neuroscience laboratories at Columbia University.

Staff

René Hen, PhD	Professor
Peter Balsam, MD/PhD	Professor
Karen Duff, PhD	Professor
Joshua Gordon, MD/PhD	Assistant Professor / Psychiatrist
Andreas H. Kottmann, PhD	Assistant Professor
Kathleen Taylor, PhD	Assistant Professor
E. David Leonardo, MD/PhD	Assistant Professor / Psychiatrist
Holly Moore, PhD	Assistant Professor
Alex Dranovsky, MD/PhD	Assistant Professor / Psychiatrist
Mark Opler, PhD	Assistant Professor
Victoria Cressman, PhD	Assistant Professor
Luis E Gonzalez, PhD	Research Scientist
Amar Sahay, PhD	Research Scientist
Michael Drew, PhD	Research Scientist
Mark Alter, MD/PhD	Research Fellow / Psychiatrist
Susanne Ahmari, MD/PhD	Research Fellow / Psychiatrist
Collin O'Carroll, PhD	Research Fellow
Nesha Burghardt, PhD	Research Fellow
Ryan Ward, PhD	Research Fellow
Salomao Segal, PhD	Research Fellow
Benjamin Samuels, PhD	Research Fellow
Maria J Perez, PhD	Postdoctoral Research Scientist

Torfi Sigursson, PhD
Sarah Marshall, PhD
Katya Likhtik, PhD

Postdoctoral Research Scientist
Postdoctoral Research Fellow
Postdoctoral Research Fellow

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-HT_{1A}R) that lead to a phenotype of increased anxiety-related behavior. We have previously identified functional abnormalities in the hippocampus of 5-HT_{1A}R knockouts, suggesting that hippocampal dysfunction plays a role in the anxiety-related phenotype in 5-HT_{1A}R-deficient mice. The group has recently extended these findings to include analysis of the communication between the hippocampus and the medial prefrontal cortex in both wild-type and 5-HT_{1A}R knockouts, demonstrating that this pathway plays a role in anxiety. A paper describing these results has been submitted. In addition, in a collaboration with Dr. Lorna Role, the lab has 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, the lab has begun to examine hippocampal and medial prefrontal cortex activity in mice carrying a genetic deletion homologous to one which causes schizophrenia in humans.

MOORE LAB: 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 malfunction 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, and to determine how development of these circuits is altered by genetic alterations or environmental exposures known to increase the risk for specific psychiatric disorders. Along these lines, the Moore laboratory conducts research on 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, the Moore lab uses anatomical, in vivo neurochemical and neurophysiological and behavioral techniques. Description of the progress made during the 2007-2008 year is as follows:

Ontogeny of corticolimbic circuits. The Moore lab has completed initial phases of two studies showing significant remodeling of limbic circuits during adolescence in the rat. Specifically, they have shown that the density of dendritic spines on projection neurons of the subiculum, the major output region of the hippocampal complex, changes significantly across postnatal development (Cressman et al., in preparation). These studies are by extended with quantification of changes in synaptic proteins that may regulate the early juvenile (postnatal day 16-25) proliferation and adolescent (P35-adulthood) pruning of dendritic spines in this region (Cressman et al., in preparation). Also completed is a study, using a combination of retrograde and anterograde tract-tracing techniques, and gene expression profiling, to characterize changes in prefrontal cortical and thalamic inputs to the amygdala during early and late adolescence (Cressman et al., 2007; Cressman et al., submitted). 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 underlie the progressive increase in risk for anxiety and addiction disorders during adolescence. These studies are being followed up with functional assessments of these circuits using electrophysiological and behavioral techniques. A third set of developmental studies, conducted in collaboration with the Division of Developmental Neuroscience, has characterized the neural and pharmacological substrates of infant vocalization in the rat, particularly vocalizations modulated by recent social experience (Muller et al., 2008; Muller et al., in press; Shair et al., in press). Taken together, the above studies provide information on normative

development of circuits that mediate the emotional and cognitive processes affected in a number of psychiatric disorders.

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, *Biological Psychiatry*, 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. Experiments conducted in the past year have confirmed that developmental neurons in the CA1 and subicular subregions of the hippocampus develop abnormally in this model exhibit morphology (decreased dendritic spine density) similar to what is reported in schizophrenia. Moreover, 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). Taken together with electrophysiological and imaging studies (Remole et al., 2007), these studies have begun to characterize candidate mechanisms underlying the abnormal activity in hippocampal activity in this model. The hippocampal activity and the responsiveness of behavior and the mesolimbic DA system to amphetamine are inter-related phenotypes highly relevant to schizophrenia (Schobel et al., submitted). The MAM E17 shows abnormal increases in both of these phenotypes (Moore et al., *Biological Psychiatry*, 2006; Remole et al., 2007). Molecular mechanisms underlying the preferential maldevelopment of limbic-related cortical circuits by MAM E17 exposure have also been examined and led to a focus on genes related to DNA repair, neurite development and specific ion conductances.

The Moore laboratory also studies a number of genetic mouse models with schizophrenia-related neural or psychopathology. In collaboration with Stephen Rayport, MD (Division of Molecular Therapeutics) they have found that in the GLS 1 heterozygote, a mouse model with a deficit in glutamate recycling developed by the Rayport laboratory, hippocampal activity and response to psychostimulants are blunted. This may indicate that limiting glutamate synthesis or release may have produced antipsychotic effects (Gaisler-Solomon et al., 2007; submitted). In addition, 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 models of cerebral cortical interneuron pathology relevant to schizophrenia. Their recent studies have shown that signaling pathways mediated by cyclin D2 and sonic hedgehog in the medial ganglionic eminence of the embryonic forebrain are important for the determination of the parvalbumin (PV)-expressing interneurons in the cortex (Glickstein et al., 2007; Xu et al., submitted). Current experiments in these models are aimed at characterizing the deficit in GABAergic inhibitory transmission in limbic cortical circuits and its ultimate effect on seizure susceptibility, affective behaviors and the response to psychostimulants. Studies in the MAM E17 and genetic mouse models reveal specific

molecular pathways or neuronal subpopulations that may mediate dysfunction of frontal and limbic cortical circuits affected in schizophrenia.

DRANOVSKY AND LEONARDO LAB: Drs. 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:

- 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.
- 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.

DUFF LAB: The main focus of Dr. Duff's work is to examine mechanisms involved in the development of neurodegenerative diseases (Alzheimer's, Parkinson's, Tauopathies etc) and to test therapeutic approaches that may attenuate disease progression. Over the last 20 years, Dr. Duff has used genetic engineering technology to create several mouse models for AD that develop either plaques or tangles. The mice that form amyloid plaques have been especially well used to examine different aspects of AD, from the development of methods for MRI based diagnosis of amyloidosis, to understanding mechanisms by which the brain degenerates. In addition, the mouse models have been used to study how possible therapeutic strategies may help in the treatment, or prevention of AD. Currently, her main interest is in exploring how tangles form in the AD brain, again using mouse models that she has created. She has recently shown that kinase inhibition aimed at reducing toxic forms of the protein tau, may be effective at reducing tangle formation in the mice. The therapeutic work has expanded to looking at the impact of hsp90 inhibitors and aggregation inhibitors for the clearance of tau.

BALSAM LAB: The lab is studying the mechanisms of adaptive behavior and how they might be altered in animal models of psychiatric disorders. In an NIMH funded project the lab studies how animals learn about time and use it to guide behavior. Additionally, this project examines how temporal information processing is changed by alterations in dopaminergic function. One project along these lines being done in collaboration with the labs of Dr. Eric Kandel and Christoph Kellendonk of Columbia University is

analyzing and seeking to remediate the timing and motivational deficits found in a transgenic mouse line that like schizophrenic patients, exhibits an increased level of dopamine D2 receptor activity in the striatum. In a related NIDA funded project the lab is studying how dopaminergic function changes over the course of learning in collaboration with Dr. Jon Horvitz (City College) and Dr. Mark West (Rutgers University). The lab is also examining the brain circuits involved in temporal information processing in studies that employ transcranial magnetic stimulation to alter cortical function. These latter studies are funded by DARPA and done in collaboration with Dr. Holly Lisanby (Division of Brain Stimulation).

KOTTMANN LAB: The Kottmann laboratory employs a variety of molecular, pharmacological, cellular and genetic loss and gain of function strategies in mice to define the neuronal contribution towards the regulation of stem cell maintenance and/or differentiation in the adult forebrain. Recently the lab has demonstrated that the induction of physiological cell stress in cholinergic cell populations in the striatum causes alterations in cell fate determination in the neurogenic niche of the SVZ. Using a combination of temporally and spatially controlled genetic gene ablation with gain of function approaches lab researchers showed that differential expression of sonic hedgehog (SHH), a morphogen well known from its involvement in the differentiation of the CNS during development, causes the observed alterations in SVZ neurogenesis. Further experimentation revealed that Shh expression in mesencephalic dopamine neurons is upregulated by physiological cell stress in cholinergic neurons which are monosynaptically connected with dopamine neurons. Mesencephalically expressed Shh acts thereby as a sentinel for basal ganglia dysfunction and at the same time alters qualitative outcome of SVZ neurogenesis causing an altered cyto-architecture of the olfactory bulb. Current efforts are directed to understanding whether altered Shh signaling from dopamine neurons to the SVZ causes the production of distinct cholinergic and dopaminergic neuronal identities in addition to neurons that migrate into the olfactory bulb. These studies might act as a guide to novel approaches to stimulate in vivo resident stem cells to give rise to particular cell identities for which a physiological need exists in particular psychiatric and neurodegenerative conditions.

In the course of these studies the Kottmann Lab produced two novel models of neurodegenerative diseases in mice: The genetic ablation of Wolframin 1, a cell physiological stress response factor expressed in basal brain structures and hippocampus, yielded a progressive, genetic model of Wolfram Syndrome, a fatal neurodegenerative disease associated with severe psychiatric complications. Haploid insufficiency for wolframin1, which is associated with increased risk for depression in humans, causes habituation deficits in the absence of overt neurodegeneration in mice. The conditional ablation of Shh from differentiated mesencephalic dopamine neurons yielded a model for progressive loss of cholinergic neurons in the striatum and dopamine neurons in the substantia nigra and ventral tegmental area. Both mouse lines are being made available by Columbia University for drug screening and validation efforts that aim for the identification of neuroprotective agents.

In collaboration with Dr. Stuart Firestein's group (Department of Biology, Columbia University) the lab has begun to analyze olfactory acuity in its mutant animals hypothesizing that Shh dysregulation could cause the olfactory dysfunction that is a preclinical sign in many neurodegenerative and psychiatric diseases. The Kottmann Lab collaborates with the lab of Dr. Serge Przedborski to determine whether Shh signaling renders mesencephalic dopamine neurons more resistant to dopaminergic neurotoxins like MPTP and 6-OHDA. Finally, the Kottmann Lab maintains close ties with the Center for Motor Neuron Biology and Disease and investigates whether differential expression of Shh by cranial somatic motor neurons distinguishes motor neurons that resist degeneration in Amyotrophic lateral sclerosis (ALS) from such that succumb to the disease.

Grant Awards

René Hen

2008 NIMH R01 MH068542-6 "Cellular Mechanisms of Antidepressant Action.

Andreas Kottmann

2008 Center for Motor Neuron Biology and Disease, Columbia University

2008 ALS Association

2007 NINDS R21 NS056312-01A1

2007 American Parkinson Disease Association (APDA)

Joshua Gordon

2008 NIMH R01 MH081968 "Neural mechanisms of increased anxiety in serotonin 1A receptor-deficient mice."

Awards and Honors

René Hen

René Hen – NIH 2008 MERIT Award

Publications

Balsam Lab

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Gordon Lab

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Kottmann Lab

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Moore Lab

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